



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 39/395, 48/00, C12P 19/34, C12Q 1/68, G01N 33/53, 33/574, 33/546, 33/567</b>	<b>A1</b>	<b>(11) International Publication Number: WO 00/23111</b> <b>(43) International Publication Date: 27 April 2000 (27.04.00)</b>
<b>(21) International Application Number:</b> PCT/US99/24331 <b>(22) International Filing Date:</b> 19 October 1999 (19.10.99)  <b>(30) Priority Data:</b> 60/104,737 19 October 1998 (19.10.98) US  <b>(71) Applicant (for all designated States except US):</b> DIADEXUS LLC [US/US]; 3303 Octavius Drive, Santa Clara, CA 95054 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SALCEDA, Susana [AR/US]; 4118 Crescendo Avenue, San Jose, CA 95136 (US). RECIPON, Herve [FR/US]; 85 Fortuna Avenue, San Francisco, CA 94115 (US). CAFFERKEY, Robert [IE/US]; Apartment #218, 350 Elan Village Lane, San Jose, CA 95134 (US).  <b>(74) Agents:</b> LICATA, Jane, Massey et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).		<b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHOD OF DIAGNOSING, MONITORING, STAGING, IMAGING AND TREATING PROSTATE CANCER  <b>(57) Abstract</b>  The present invention provides new methods for detecting, diagnosing, monitoring, staging, prognosticating, imaging and treating prostate cancer.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

**METHOD OF DIAGNOSING,  
MONITORING, STAGING, IMAGING AND TREATING PROSTATE CANCER**

**FIELD OF THE INVENTION**

This invention relates, in part, to newly developed  
5 assays for detecting, diagnosing, monitoring, staging,  
prognosticating, imaging and treating cancers, particularly  
prostate cancer.

**BACKGROUND OF THE INVENTION**

Cancer of the prostate is the most prevalent malignancy  
10 in adult males, excluding skin cancer, and is an increasingly  
prevalent health problem in the United States. In 1996, it  
was estimated that 41,400 deaths would result from this  
disease in the United States alone, indicating that prostate  
cancer is second only to lung cancer as the most common cause  
15 of death in the same population. If diagnosed and treated  
early, when the cancer is still confined to the prostate, the  
chances of cure is significantly higher.

Treatment decisions for an individual are linked to the  
stage of prostate cancer present in that individual. A common  
20 classification of the spread of prostate cancer was developed  
by the American Urological Association (AUA). The AUA system  
divides prostate tumors into four stages, A to D. Stage A,  
microscopic cancer within prostate, is further subdivided into  
stages A1 and A2. Sub-stage A1 is a well-differentiated  
25 cancer confined to one site within the prostate. Treatment  
is generally observation, radical prostatectomy, or radiation.  
Sub-stage A2 is a moderately to poorly differentiated cancer  
at multiple sites within the prostate. Treatment is radical  
prostatectomy or radiation. Stage B, palpable lump within the  
30 prostate, is also further subdivided into sub-stages B1 and  
B2. In sub-stage B1, the cancer forms a small nodule in one

- 2 -

lobe of the prostate. In sub-stage B2, the cancer forms large or multiple nodules, or occurs in both lobes of the prostate. Treatment for sub-stages B1 and B2 is either radical prostatectomy or radiation. Stage C is a large cancer mass  
5 involving most or all of the prostate and is also further subdivided into two sub-stages. In sub-stage C1, the cancer forms a continuous mass that may have extended beyond the prostate. In sub-stage C2, the cancer forms a continuous mass that invades the surrounding tissue. Treatment for both these  
10 sub-stages is radiation with or without drugs to address the cancer. The fourth stage, Stage D is metastatic cancer and is also subdivided into two sub-stages. In sub-stage D1, the cancer appears in the lymph nodes of the pelvis. In sub-stage D2, the cancer involves tissues beyond lymph nodes. Treatment  
15 for both of these sub-stages is systemic drugs to address the cancer as well as pain.

However, current prostate cancer staging methods are limited. As many as 50% of prostate cancers initially staged as A2, B, or C are actually stage D, metastatic. Discovery  
20 of metastasis is significant because patients with metastatic cancers have a poorer prognosis and require significantly different therapy than those with localized cancers. The five year survival rates for patients with localized and metastatic prostate cancers are 93% and 29%, respectively.

25 Accordingly, there is a great need for more sensitive and accurate methods for the staging of a cancer in a human to determine whether or not such cancer has metastasized and for monitoring the progress of a cancer in a human which has not metastasized for the onset of metastasis.

30 It has now been found that a number of proteins in the public domain are useful as diagnostic markers for prostate cancer. These diagnostic markers are referred to herein as cancer specific genes or CSGs and include, but are not limited to: Prol09 which is a human zinc- $\alpha$  2-glycoprotein (Freje et  
35 al. Genomics 1993 18(3):575-587); Prol12 which is a human

- 3 -

cysteine-rich protein with a zinc-finger motif (Liebhaber et al. Nucleic Acid Research 1990 18(13):3871-3879; WO9514772 and WO9845436); Prol11 which is a prostate-specific transglutaminase (Dubbink et al. Genomics 1998 51(3):434-444);

5 Prol15 which is a novel serine protease with transmembrane, LDLR, and SRCR domains and maps to 21q22.3 (Paoloni-Giacobino et al. Genomics 1997 44(3):309-320; WO9837418 and WO987093); Prol10 which is a human breast carcinoma fatty acid synthase (U.S. Patent 5,665,874 and WO9403599); Prol13 which is a

10 homeobox gene, HOXB13 (Steinicki et al. J. Invest. Dermatol. 1998 111:57-63); Prol14 which is a human tetraspan NET-1 (WO9839446); and Prol18 which is a human JM27 protein (WO9845435). ESTs for these CSGs are set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13 and 15 while the full length contigs for

15 these CSGs are set forth in SEQ ID NO:2, 4, 6, 8, 10, 12, 14 and 16, respectively. Additional CSGs for use in the present invention are depicted herein in SEQ ID NO: 17, 18, 19 and 20.

In the present invention, methods are provided for detecting, diagnosing, monitoring, staging, prognosticating,

20 imaging and treating prostate cancer via the cancer specific genes referred to herein as CSGs. For purposes of the present invention, CSG refers, among other things, to native protein expressed by the gene comprising a polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

25 16, 17, 18, 19 or 20. By "CSG" it is also meant herein polynucleotides which, due to degeneracy in genetic coding, comprise variations in nucleotide sequence as compared to SEQ ID NO: 1-20, but which still encode the same protein. In the alternative, what is meant by CSG as used herein, means the

30 native mRNA encoded by the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, levels of the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or

35 20, or levels of a polynucleotide which is capable of

- 4 -

hybridizing under stringent conditions to the antisense sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

#### SUMMARY OF THE INVENTION

Toward these ends, and others, it is an object of the present invention to provide a method for diagnosing the presence of prostate cancer by analyzing for changes in levels of CSG in cells, tissues or bodily fluids compared with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control, wherein a change in levels of CSG in the patient versus the normal human control is associated with prostate cancer.

Further provided is a method of diagnosing metastatic prostate cancer in a patient having prostate cancer which is not known to have metastasized by identifying a human patient suspected of having prostate cancer that has metastasized; analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing the CSG levels in such cells, tissues, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control, wherein an increase in CSG levels in the patient versus the normal human control is associated with prostate cancer which has metastasized.

- 5 -

Also provided by the invention is a method of staging prostate cancer in a human which has such cancer by identifying a human patient having such cancer; analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing CSG levels in such cells, tissues, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control sample, wherein an increase in CSG levels in the patient versus the normal human control is associated with a cancer which is progressing and a decrease in the levels of CSG is associated with a cancer which is regressing or in remission.

Further provided is a method of monitoring prostate cancer in a human having such cancer for the onset of metastasis. The method comprises identifying a human patient having such cancer that is not known to have metastasized; periodically analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing the CSG levels in such cells, tissue, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control sample, wherein an increase in CSG levels in the patient versus the normal human control is associated with a cancer which has metastasized.

Further provided is a method of monitoring the change in stage of prostate cancer in a human having such cancer by looking at levels of CSG in a human having such cancer. The method comprises identifying a human patient having such cancer; periodically analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing the CSG levels in such cells, tissue, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control sample, wherein an increase in CSG levels in the patient versus the normal human control is associated with a cancer which is progressing and a decrease in the levels of CSG is associated with a cancer which is regressing or in remission.

- 6 -

Further provided are methods of designing new therapeutic agents targeted to a CSG for use in imaging and treating prostate cancer. For example, in one embodiment, therapeutic agents such as antibodies targeted against CSG or  
5 fragments of such antibodies can be used to detect or image localization of CSG in a patient for the purpose of detecting or diagnosing a disease or condition. Such antibodies can be polyclonal, monoclonal, or omniclonal or prepared by molecular biology techniques. The term "antibody", as used herein and  
10 throughout the instant specification is also meant to include aptamers and single-stranded oligonucleotides such as those derived from an *in vitro* evolution protocol referred to as SELEX and well known to those skilled in the art. Antibodies can be labeled with a variety of detectable labels including,  
15 but not limited to, radioisotopes and paramagnetic metals. Therapeutics agents such as antibodies or fragments thereof can also be used in the treatment of diseases characterized by expression of CSG. In these applications, the antibody can be used without or with derivatization to a cytotoxic agent  
20 such as a radioisotope, enzyme, toxin, drug or a prodrug.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be understood, however, that the following description and the  
25 specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and  
30 from reading the other parts of the present disclosure.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to diagnostic assays and methods, both quantitative and qualitative for detecting, diagnosing, monitoring, staging and prognosticating cancers



- 7 -

by comparing levels of CSG in a human patient with those of CSG in a normal human control. For purposes of the present invention, what is meant by CSG levels is, among other things, native protein expressed by the gene comprising a polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. By "CSG" it is also meant herein polynucleotides which, due to degeneracy in genetic coding, comprise variations in nucleotide sequence as compared to SEQ ID NO: 1-20, but which still encode the same protein. The native protein being detected, may be whole, a breakdown product, a complex of molecules or chemically modified. In the alternative, what is meant by CSG as used herein, means the native mRNA encoded by the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, levels of the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, or levels of a polynucleotide which is capable of hybridizing under stringent conditions to the antisense sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. Such levels are preferably determined in at least one of, cells, tissues and/or bodily fluids, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for diagnosing overexpression of CSG protein compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of prostate cancer.

All the methods of the present invention may optionally include determining the levels of other cancer markers as well as CSG. Other cancer markers, in addition to CSG, useful in the present invention will depend on the cancer being tested and are known to those of skill in the art.

- 8 -

**Diagnostic Assays**

The present invention provides methods for diagnosing the presence of prostate cancer by analyzing for changes in levels of CSG in cells, tissues or bodily fluids compared with levels of CSG in cells, tissues or bodily fluids of preferably the same type from a normal human control, wherein an increase in levels of CSG in the patient versus the normal human control is associated with the presence of prostate cancer.

Without limiting the instant invention, typically, for a quantitative diagnostic assay a positive result indicating the patient being tested has cancer is one in which cells, tissues or bodily fluid levels of the cancer marker, such as CSG, are at least two times higher, and most preferably are at least five times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control.

The present invention also provides a method of diagnosing metastatic prostate cancer in a patient having prostate cancer which has not yet metastasized for the onset of metastasis. In the method of the present invention, a human cancer patient suspected of having prostate cancer which may have metastasized (but which was not previously known to have metastasized) is identified. This is accomplished by a variety of means known to those of skill in the art.

In the present invention, determining the presence of CSG levels in cells, tissues or bodily fluid, is particularly useful for discriminating between prostate cancer which has not metastasized and prostate cancer which has metastasized. Existing techniques have difficulty discriminating between prostate cancer which has metastasized and prostate cancer which has not metastasized and proper treatment selection is often dependent upon such knowledge.

In the present invention, the cancer marker levels measured in such cells, tissues or bodily fluid is CSG, and are compared with levels of CSG in preferably the same cells, tissue or bodily fluid type of a normal human control. That

- 9 -

is, if the cancer marker being observed is just CSG in serum, this level is preferably compared with the level of CSG in serum of a normal human control. An increase in the CSG in the patient versus the normal human control is associated with prostate cancer which has metastasized.

Without limiting the instant invention, typically, for a quantitative diagnostic assay a positive result indicating the cancer in the patient being tested or monitored has metastasized is one in which cells, tissues or bodily fluid levels of the cancer marker, such as CSG, are at least two times higher, and most preferably are at least five times higher, than in preferably the same cells, tissues or bodily fluid of a normal patient.

Normal human control as used herein includes a human patient without cancer and/or non cancerous samples from the patient; in the methods for diagnosing or monitoring for metastasis, normal human control may preferably also include samples from a human patient that is determined by reliable methods to have prostate cancer which has not metastasized.

#### 20 **Staging**

The invention also provides a method of staging prostate cancer in a human patient. The method comprises identifying a human patient having such cancer and analyzing cells, tissues or bodily fluid from such human patient for CSG. The CSG levels determined in the patient are then compared with levels of CSG in preferably the same cells, tissues or bodily fluid type of a normal human control, wherein an increase in CSG levels in the human patient versus the normal human control is associated with a cancer which is progressing and a decrease in the levels of CSG (but still increased over true normal levels) is associated with a cancer which is regressing or in remission.

#### **Monitoring**

Further provided is a method of monitoring prostate cancer in a human patient having such cancer for the onset of

- 10 -

metastasis. The method comprises identifying a human patient having such cancer that is not known to have metastasized; periodically analyzing cells, tissues or bodily fluid from such human patient for CSG; and comparing the CSG levels  
5 determined in the human patient with levels of CSG in preferably the same cells, tissues or bodily fluid type of a normal human control, wherein an increase in CSG levels in the human patient versus the normal human control is associated with a cancer which has metastasized. In this method, normal  
10 human control samples may also include prior patient samples.

Further provided by this invention is a method of monitoring the change in stage of prostate cancer in a human patient having such cancer. The method comprises identifying a human patient having such cancer; periodically analyzing  
15 cells, tissues or bodily fluid from such human patient for CSG; and comparing the CSG levels determined in the human patient with levels of CSG in preferably the same cells, tissues or bodily fluid type of a normal human control, wherein an increase in CSG levels in the human patient versus  
20 the normal human control is associated with a cancer which is progressing in stage and a decrease in the levels of CSG is associated with a cancer which is regressing in stage or in remission. In this method, normal human control samples may also include prior patient samples.

25 Monitoring a patient for onset of metastasis is periodic and preferably done on a quarterly basis. However, this may be more or less frequent depending on the cancer, the particular patient, and the stage of the cancer.

#### **Assay Techniques**

30 Assay techniques that can be used to determine levels of gene expression (including protein levels), such as CSG of the present invention, in a sample derived from a patient are well known to those of skill in the art. Such assay methods include, without limitation, radioimmunoassays, reverse  
35 transcriptase PCR (RT-PCR) assays, immunohistochemistry

- 11 -

assays, *in situ* hybridization assays, competitive-binding assays, Western Blot analyses, ELISA assays and proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel based approaches such as mass spectrometry or protein interaction profiling. Among these, ELISAs are frequently preferred to diagnose a gene's expressed protein in biological fluids.

An ELISA assay initially comprises preparing an antibody, if not readily available from a commercial source, specific to CSG, preferably a monoclonal antibody. In addition a reporter antibody generally is prepared which binds specifically to CSG. The reporter antibody is attached to a detectable reagent such as radioactive, fluorescent or enzymatic reagent, for example horseradish peroxidase enzyme or alkaline phosphatase.

To carry out the ELISA, antibody specific to CSG is incubated on a solid support, e.g. a polystyrene dish, that binds the antibody. Any free protein binding sites on the dish are then covered by incubating with a non-specific protein such as bovine serum albumin. Next, the sample to be analyzed is incubated in the dish, during which time CSG binds to the specific antibody attached to the polystyrene dish. Unbound sample is washed out with buffer. A reporter antibody specifically directed to CSG and linked to a detectable reagent such as horseradish peroxidase is placed in the dish resulting in binding of the reporter antibody to any monoclonal antibody bound to CSG. Unattached reporter antibody is then washed out. Reagents for peroxidase activity, including a colorimetric substrate are then added to the dish. Immobilized peroxidase, linked to CSG antibodies, produces a colored reaction product. The amount of color developed in a given time period is proportional to the amount of CSG protein present in the sample. Quantitative results typically are obtained by reference to a standard curve.

- 12 -

A competition assay can also be employed wherein antibodies specific to CSG are attached to a solid support and labeled CSG and a sample derived from the host are passed over the solid support. The amount of label detected which is  
5 attached to the solid support can be correlated to a quantity of CSG in the sample.

Nucleic acid methods can also be used to detect CSG mRNA as a marker for prostate cancer. Polymerase chain reaction (PCR) and other nucleic acid methods, such as ligase chain  
10 reaction (LCR) and nucleic acid sequence based amplification (NASABA), can be used to detect malignant cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population  
15 in a complex mixture of thousands of other mRNA species. In RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction. RT-PCR can thus reveal by amplification the  
20 presence of a single species of mRNA. Accordingly, if the mRNA is highly specific for the cell that produces it, RT-PCR can be used to identify the presence of a specific type of cell.

Hybridization to clones or oligonucleotides arrayed on  
25 a solid support (i.e. gridding) can be used to both detect the expression of and quantitate the level of expression of that gene. In this approach, a cDNA encoding the CSG gene is fixed to a substrate. The substrate may be of any suitable type including but not limited to glass, nitrocellulose, nylon or  
30 plastic. At least a portion of the DNA encoding the CSG gene is attached to the substrate and then incubated with the analyte, which may be RNA or a complementary DNA (cDNA) copy of the RNA, isolated from the tissue of interest. Hybridization between the substrate bound DNA and the analyte  
35 can be detected and quantitated by several means including but

- 13 -

not limited to radioactive labeling or fluorescence labeling of the analyte or a secondary molecule designed to detect the hybrid. Quantitation of the level of gene expression can be done by comparison of the intensity of the signal from the  
5 analyte compared with that determined from known standards. The standards can be obtained by *in vitro* transcription of the target gene, quantitating the yield, and then using that material to generate a standard curve.

Of the proteomic approaches, 2D electrophoresis is a  
10 technique well known to those in the art. Isolation of individual proteins from a sample such as serum is accomplished using sequential separation of proteins by different characteristics usually on polyacrylamide gels. First, proteins are separated by size using an electric  
15 current. The current acts uniformly on all proteins, so smaller proteins move farther on the gel than larger proteins. The second dimension applies a current perpendicular to the first and separates proteins not on the basis of size but on the specific electric charge carried by each protein. Since  
20 no two proteins with different sequences are identical on the basis of both size and charge, the result of a 2D separation is a square gel in which each protein occupies a unique spot. Analysis of the spots with chemical or antibody probes, or subsequent protein microsequencing can reveal the relative  
25 abundance of a given protein and the identity of the proteins in the sample.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a  
30 patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy material. Bodily fluids useful in the present invention include blood, urine, saliva or any other bodily secretion or derivative thereof. By blood it is meant to include whole blood, plasma, serum or any derivative of  
35 blood.

- 14 -

***In Vivo Targeting of CSGs***

Identification of these CSGs is also useful in the rational design of new therapeutics for imaging and treating cancers, and in particular prostate cancer. For example, in one embodiment, antibodies which specifically bind to CSG can be raised and used *in vivo* in patients suspected of suffering from prostate cancer. Antibodies which specifically bind a CSG can be injected into a patient suspected of having prostate cancer for diagnostic and/or therapeutic purposes.

The preparation and use of antibodies for *in vivo* diagnosis is well known in the art. For example, antibody-chelators labeled with Indium-111 have been described for use in the radioimmunoscentigraphic imaging of carcinoembryonic antigen expressing tumors (Sumerdon et al. Nucl. Med. Biol. 1990 17:247-254). In particular, these antibody-chelators have been used in detecting tumors in patients suspected of having recurrent colorectal cancer (Griffin et al. J. Clin. Onc. 1991 9:631-640). Antibodies with paramagnetic ions as labels for use in magnetic resonance imaging have also been described (Lauffer, R.B. Magnetic Resonance in Medicine 1991 22:339-342). Antibodies directed against CSG can be used in a similar manner. Labeled antibodies which specifically bind CSG can be injected into patients suspected of having prostate cancer for the purpose of diagnosing or staging of the disease status of the patient. The label used will be selected in accordance with the imaging modality to be used. For example, radioactive labels such as Indium-111, Technetium-99m or Iodine-131 can be used for planar scans or single photon emission computed tomography (SPECT). Positron emitting labels such as Fluorine-19 can be used in positron emission tomography. Paramagnetic ions such as Gadlinium (III) or Manganese (II) can be used in magnetic resonance imaging (MRI). Localization of the label permits determination of the spread of the cancer. The amount of label within an organ or



- 15 -

tissue also allows determination of the presence or absence of cancer in that organ or tissue.

For patients diagnosed with prostate cancer, injection of an antibody which specifically binds CSG can also have a therapeutic benefit. The antibody may exert its therapeutic effect alone. Alternatively, the antibody can be conjugated to a cytotoxic agent such as a drug, toxin or radionuclide to enhance its therapeutic effect. Drug monoclonal antibodies have been described in the art for example by Garnett and Baldwin, Cancer Research 1986 46:2407-2412. The use of toxins conjugated to monoclonal antibodies for the therapy of various cancers has also been described by Pastan et al. Cell 1986 47:641-648. Yttrium-90 labeled monoclonal antibodies have been described for maximization of dose delivered to the tumor while limiting toxicity to normal tissues (Goodwin and Meares Cancer Supplement 1997 80:2675-2680). Other cytotoxic radionuclides including, but not limited to Copper-67, Iodine-131 and Rhenium-186 can also be used for labeling of antibodies against CSG.

Antibodies which can be used in these *in vivo* methods include polyclonal, monoclonal and omniclonal antibodies and antibodies prepared via molecular biology techniques. Antibody fragments and aptamers and single-stranded oligonucleotides such as those derived from an *in vitro* evolution protocol referred to as SELEX and well known to those skilled in the art can also be used.

Small molecules predicted via computer imaging to specifically bind to regions of CSGs can also be designed and synthesized and tested for use in the imaging and treatment of prostate cancer. Further, libraries of molecules can be screened for potential anticancer agents by assessing the ability of the molecule to bind to CSGs identified herein. Molecules identified in the library as being capable of binding to CSG are key candidates for further evaluation for use in the treatment of prostate cancer.

- 16 -

**EXAMPLES**

The present invention is further described by the following examples. These examples are provided solely to illustrate the invention by reference to specific embodiments.

5 These exemplifications, while illustrating certain aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

All examples outlined here were carried out using standard techniques, which are well known and routine to those  
10 of skill in the art, except where otherwise described in detail. Routine molecular biology techniques of the following example can be carried out as described in standard laboratory manuals, such as Sambrook et al., MOLECULAR CLONING: A LABORATORY MANUAL, 2nd Ed.; Cold Spring Harbor Laboratory  
15 Press, Cold Spring Harbor, N.Y. (1989).

**Example 1: Identification of CSGs**

Identification of CSGs were carried out by a systematic analysis of data in the LIFESEQ database available from Incyte Pharmaceuticals, Palo Alto, CA, using the data mining Cancer  
20 Leads Automatic Search Package (CLASP) developed by diaDexus LLC, Santa Clara, CA.

The CLASP performs the following steps: selection of highly expressed organ specific genes based on the abundance level of the corresponding EST in the targeted organ versus  
25 all the other organs; analysis of the expression level of each highly expressed organ specific genes in normal, tumor tissue, disease tissue and tissue libraries associated with tumor or disease; selection of the candidates demonstrating component ESTs were exclusively or more frequently found in tumor  
30 libraries. The CLASP allows the identification of highly expressed organ and cancer specific genes. A final manual in depth evaluation is then performed to finalize the CSGs selection.

- 17 -

Clones depicted in the following Table 1 are CSGs useful in diagnosing, monitoring, staging, imaging and treating prostate cancer.

**Table 1: CSGs**

5	Clone ID	Pro #	SEQ ID NO:
	3424528H1	Pro109	1,2
	578349H1	Pro112	3,4
	1794013H1	Pro111	5,6
	2189835H1	Pro115	7,8
10	3277219H1	Pro110	9,10
	1857415	Pro113	11,12
	1810463H1	Pro114	13,14
	zr65G11	Pro118	15,16
	2626135H1		17
15	zd46d08		18
	1712252H1		19
	784583H1		20

**Example 2: Relative Quantitation of Gene Expression**

20 Real-Time quantitative PCR with fluorescent Taqman probes is a quantitation detection system utilizing the 5'-3' nuclease activity of Taq DNA polymerase. The method uses an internal fluorescent oligonucleotide probe (Taqman) labeled with a 5' reporter dye and a downstream, 3' quencher dye.

25 During PCR, the 5'-3' nuclease activity of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA).

Amplification of an endogenous control is used to standardize the amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous

- 18 -

control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation relative to the "calibrator" can be obtained  
5 using the standard curve method or the comparative method (User Bulletin #2: ABI PRISM 7700 Sequence Detection System).

The tissue distribution and the level of the target gene were evaluated for every sample in normal and cancer tissues. Total RNA was extracted from normal tissues, cancer tissues,  
10 and from cancers and the corresponding matched adjacent tissues. Subsequently, first strand cDNA was prepared with reverse transcriptase and the polymerase chain reaction was done using primers and Taqman probes specific to each target gene. The results were analyzed using the ABI PRISM 7700  
15 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

**Expression of Clone ID 3424528H1 (Pro109):**

For the CSG Pro109, real-time quantitative PCR was  
20 performed using the following primers:

Forward Primer:

5' - ATCAGAACAAAGAGGCTGTGTC - 3' (SEQ ID NO:21)

Reverse Primer:

5' - ATCTCTAAAGCCCCAACCTTC - 3' (SEQ ID NO:22)

25 The absolute numbers depicted in Table 2 are relative levels of expression of the CSG referred to as Pro109 in 12 normal different tissues. All the values are compared to normal stomach (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular  
30 tissue from different individuals.

- 19 -

**Table 2: Relative Levels of CSG Prol09 Expression in Pooled Samples**

Tissue	NORMAL
Colon	0.02
Endometrium	0.01
Kidney	0.48
Liver	14.83
Ovary	0.08
Pancreas	4.38
Prostate	11.24
Small Intestine	0.42
Spleen	0
Stomach	1
Testis	0.62
Uterus	0.02

The relative levels of expression in Table 2 show that with the exception of liver (14.83), Prol09 mRNA expression is higher (11.24) in prostate compared with all other normal tissues analyzed. Pancreas, with a relative expression level of 4.38, is the only other tissue expressing considerable mRNA for Prol09.

The absolute numbers in Table 2 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 3.

The absolute numbers depicted in Table 3 are relative levels of expression of Prol09 in 28 pairs of matching samples and 4 unmatched samples. All the values are compared to normal stomach (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

- 20 -

**Table 3: Relative Levels of CSG Pro109 Expression in Individual Samples**

	Sample ID	Tissue	Cancer	Matching Normal Adjacent
	Pro34B	Prostate 1	5.98	6.06
5	Pro65XB	Prostate 2	16.68	3.85
	Pro69XB	Prostate 3	20.46	6.82
	Pro78XB	Prostate 4	1.39	1.4
	Pro101XB	Prostate 5	24.8	9.8
	Pro12B	Prostate 6	9.1	0.2
10	Pro13XB	Prostate 7	0.5	9.7
	Pro20XB	Prostate 8	13	12.5
	Pro23B	Prostate 9	16.8	3
	Ovr100050	Ovary 1	0.4	
	Ovr1028	Ovary 2	1.9	
15	Ovr18GA	Ovary 3		0.1
	Ovr206I	Ovary 4		0.1
	Mam12X	Mammary Gland 1	13.5	1.4
	Mam47XP	Mammary Gland 2	0.7	0.2
	Lng47XQ	Lung 1	2.36	0.03
20	Lng60XL	Lung 2	7.39	0.2
	Lng75XC	Lung 3	0.77	0.27
	StoAC44	Stomach 1	0.05	1.19
	StoAC93	Stomach 2	0.55	0.8
	StoAC99	Stomach 3	0.12	3.04
25	ColAS43	Colon 1	16.11	0.07
	ColAS45	Colon 2	0.11	0.08
	ColAS46	Colon 3	4.99	0.4
	Liv15XA	Liver 1	8.43	10.97
	Liv42X	Liver 2	1.57	20.82

- 21 -

	Liv94XA	Liver 3	2.98	9.19
	Pan77X	Pancreas 1	36	32
	Pan82XP	Pancreas 2	0.09	7.09
	Pan92X	Pancreas 3	0.7	0
5	Pan71XL	Pancreas 4	2.48	0.73
	Pan10343	Pancreas 5	46	5.5

0 = Negative

In the analysis of matching samples, the higher levels of expression were in prostate, showing a high degree of tissue specificity for prostate tissue. Of all the samples different than prostate analyzed, only 4 cancer samples (the cancer sample mammary 1 with 13.5, colon 1 with 16.11, liver 1 with 8.43, and lung 2 with 7.39) showed an expression comparable to the mRNA expression in prostate. These results confirmed some degree of tissue specificity as obtained with the panel of normal pooled samples (Table 2).

Furthermore, the level of mRNA expression was compared in cancer samples and the isogenic normal adjacent tissue from the same individual. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 3 shows overexpression of Prol09 in 6 out of 9 primary prostate cancer tissues compared with their respective normal adjacents. Thus, overexpression in the cancer tissue was observed in 66.66% of the prostate matching samples tested (total of 9 prostate matching samples).

Altogether, the degree of tissue specificity, plus the mRNA overexpression in 66.66% of the primary prostate matching samples tested is indicative of Prol09 being a diagnostic marker for prostate cancer.

- 22 -

**Expression of Clone ID 578349H1 (Prol12):**

For the CSG Prol12, real-time quantitative PCR was performed using the following primers:

Forward Primer

5' - TGCCGAAGAGGTTTCAGTGC - 3' (SEQ ID NO:23)

Reverse Primer

5' - GCCACAGTGGTACTGTCCAGAT - 3' (SEQ ID NO:24)

The absolute numbers depicted in Table 4 are relative levels of expression of the CSG Prol12 in 12 normal different tissues. All the values are compared to normal thymus (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

**Table 4: Relative Levels of CSG Prol12 Expression in Pooled Samples**

<b>Tissue</b>	<b>NORMAL</b>
Brain	2.9
Heart	0.1
Kidney	0.2
Liver	0.2
Lung	7.7
Mammary	4.2
Muscle	0.1
Prostate	5.5
Small Intestine	1.8
Testis	1
Thymus	1
Uterus	21

The relative levels of expression in Table 4 show that Prol12 mRNA expression is the 3<sup>rd</sup> most highly expressed gene (after uterus and mammary) in the pool of normal prostate tissue compared to a total of 12 tissues analyzed. The absolute numbers in Table 4 were obtained analyzing pools of samples of a particular tissue from different individuals. These results demonstrate that Prol12 mRNA expression is specific for prostate thus indicating Prol12 to be a diagnostic marker for prostate disease especially cancer.



- 23 -

**Expression of Clone ID 1794013H1 (Prol11):**

For the CSG Prol11, real-time quantitative PCR was performed using the following primers:

Forward Primer

5' - GCTGCAAGTTCTCCACATTGA - 3' (SEQ ID NO:25)

Reverse Primer

5' - CAGCCGCAGGTGAAACAC - 3' (SEQ ID NO:26)

The absolute numbers depicted in Table 5 are relative levels of expression of the CSG Prol11 in 12 normal different tissues. All the values are compared to normal testis (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

**Table 5: Relative Levels of CSG Prol11 Expression in Pooled**

**Samples**

<b>Tissue</b>	<b>NORMAL</b>
Brain	0.04
Heart	0
Kidney	0
Liver	0
Lung	0.05
Mammary	0.14
Muscle	5166.6
Prostate	1483.72
Small Intestine	0.33
Testis	1
Thymus	0.49
Uterus	0.07

The relative levels of expression in Table 5 show that Prol11 mRNA expression is extraordinarily high in the pool of normal prostate (1483.72) compared to all the other tissues analyzed with the exception of muscle (5166.6). These results demonstrate that Prol11 mRNA expression shows specificity for prostate and muscle.

The absolute numbers in Table 5 were obtained analyzing pools of samples of a particular tissue from different

- 24 -

individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 6.

The absolute numbers depicted in Table 6 are relative levels of expression of Prol11 in 48 pairs of matching and 18 unmatched samples. All the values are compared to normal testis (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

**Table 6: Relative Levels of CSG Prol11 Expression in Individual Samples**

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Pro101XB	Prostate 1	8.3	21.8
Pro12B	Prostate 2	2336	133
Pro13XB	Prostate 3	3.4	23
Pro20XB	Prostate 4	21.6	121.5
Pro23B	Prostate 5	19.4	3.7
Pro34B	Prostate 6	15	39
Pro65XB	Prostate 7	8	867
Pro69XB	Prostate 8	56	94
Pro78XB	Prostate 9	24	1515
Pro84XB	Prostate 10	119	15.35
Pro90XB	Prostate 11	8.08	112.2
Pro91XB	Prostate 12	0.88	51.8
ProC215	Prostate 13	0.3	
ProC234	Prostate 14	0.35	
ProC280	Prostate 15	436.5	
Pro109XB	Prostate 16	3.43	265
Pro110	Prostate 17	18.2	8.73

- 25 -

	Pro125XB	Prostate 18	0.34	186
	Pro326	Prostate 19	1392	110
	Pro10R	Prostate 20 (prostatitis)	0.5	
	Pro20R	Prostate 21 (prostatitis)	24.1	
5	Pro258	Prostate 22 (BPH)	4610	
	Pro263C	Prostate 23 (BPH)	0	
	Pro267A	Prostate 24 (BPH)	1.46	
	Pro271A	Prostate 25 (BPH)	0	
	Pro460Z	Prostate 26 (BPH)	1.47	
10	ProC032	Prostate 27 (BPH)	14.4	
	Tst39X	Testis 1	0	0
	Bld32XK	Bladder 1	0.44	0.41
	Bld46XK	Bladder 2	0	0
	Bld66X	Bladder 3	0	0
15	BldTR14	Bladder 4	0	0
	Kid106XD	Kidney 1	0	0
	Kid107XD	Kidney 2	0	0
	Kid109XD	Kidney 3	0	0
	Pan10343	Pancreas 1	0	0
20	Pan71XL	Pancreas 2	0	0
	Pan77X	Pancreas 3	0	0
	Liv15XA	Liver 1	0	0
	Liv42X	Liver 2	0	0
	ClnAS43	Colon 1	0	0
25	ClnAS45	Colon 2	0	0
	ClnAS46	Colon 3	0	0
	ClnAS67	Colon 4	0	0
	ClnAC19	Colon 5	0	0
	ClnAS12	Colon 6	0	0

- 26 -

	SmI21XA	Small Intestine 1	0	0
	SmIH89	Small Intestine 2	0	0
	Lng47XQ	Lung 1	0.7	0
	Lng60XL	Lung 2	0	0
5	Lng75XC	Lung 3	0	0
	Lng90X	Lung 4	0	0
	Mam12X	Mammary Gland 1	0	1.4
	Mam59X	Mammary Gland 2	0.2	0
	MamA06X	Mammary Gland 3	0	0
10	MamS127	Mammary Gland 4	0	0
	Mam162X	Mammary Gland 5	0	0
	Mam42DN	Mammary Gland 6	0	0
	Ovr103X	Ovary 1	0.14	0
	Ovr10050	Ovary 2	0.2	
15	Ovr1028	Ovary 3	0	
	Ovr10400	Ovary 4	0.2	
	Ovr18GA	Ovary 5		0
	Ovr206I	Ovary 6		0
	Ovr20GA	Ovary 7		0.2
20	Ovr25GA	Ovary 8		0

0= Negative

In the analysis of matching samples, the higher levels of expression were in prostate showing a high degree of tissue specificity for prostate. These results confirm the tissue specificity results obtained with normal pooled samples (Table 5).

Furthermore, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 6 shows overexpression of Prol11 in 5 out

- 27 -

of 16 primary prostate cancer samples compared with their respective normal adjacent (prostate samples 2, 5, 10, 17, and 19). Similar expression levels were observed in 3 unmatched prostate cancers (prostate samples 13, 14, 15), 2 prostatitis (prostate samples 20, 21), and 6 benign prostatic hyperplasia samples (prostate samples 22 through 27). Thus, there is overexpression in the cancer tissue of 31.25% of the prostate matching samples tested (total of 16 prostate matching samples).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in 31.25% of the prostate matching samples tested are indicative of Prol11 being a diagnostic marker for prostate cancer.

**Expression of Clone ID 2189835H1 (Prol15):**

For the CSG Prol15, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- TGGCTTTGAACTCAGGGTCA - 3' (SEQ ID NO:27)

Reverse Primer

5'- CGGATGCACCTCGTAGACAG - 3' (SEQ ID NO:28)

The absolute numbers depicted in Table 7 are relative levels of expression of the CSG Prol15 in 12 normal different tissues. All the values are compared to normal thymus (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

**Table 7: Relative Levels of CSG Prol15 Expression in Pooled Samples**

Tissue	NORMAL
Brain	0.016
Heart	0.002
Kidney	8.08
Liver	2.20
Lung	112.99

- 28 -

Mammary	29.45
Muscle	0.05
Prostate	337.79
Small Intestine	7.54
Testis	1.48
Thymus	1
Uterus	1.4

The relative levels of expression in Table 7 show that Prol15 mRNA expression is higher (337.79) in prostate compared with all the other normal tissues analyzed. Lung, with a relative expression level of 112.99, and mammary (29.446) are the other tissues expressing moderate levels of mRNA for Prol15. These results establish Prol15 mRNA expression to be highly specific for prostate.

The absolute numbers in Table 7 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 8.

The absolute numbers depicted in Table 8 are relative levels of expression of Prol15 in 17 pairs of matching and 21 unmatched samples. All the values are compared to normal thymus (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

**Table 8: Relative Levels of CSG Prol15 Expression in Individual Samples**

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Prol2B	Prostate 1	1475.9	190.3
ProC234	Prostate 2	169.61	
Pro109XB	Prostate 3		639.53
Pro101XB	Prostate 4	1985.2	2882.9

- 29 -

5	Pro13XB	Prostate 5	34.9	13.9
	Pro215	Prostate 6	525.59	
	Pro125XB	Prostate 7		556.05
	Pro23B	Prostate 8	1891.4	1118.6
	ProC280	Prostate 9	454.3	
10	Pro20XB	Prostate 10	1332.6	
	Pro34B	Prostate 11		362.91
	Pro65XB	Prostate 12		135.06
	Pro69XB	Prostate 13		179.67
	Pro10R	Prostate 14 (prostatitis)	143.82	
15	Pro20R	Prostate 15 (prostatitis)	397.79	
	Pro258	Prostate 16 (BPH)	216.6	
	Pro263C	Prostate 17 (BPH)	601.25	
	Pro267A	Prostate 18 (BPH)	200.28	
	Pro271A	Prostate 19 (BPH)	111.43	
20	Pro460Z	Prostate 20 (BPH)	53.84	
	ProC032	Prostate 21 (BPH)	56.94	
	SmI21XA	Small Intestine 1	28.8	29.9
	SmIH89	Small Intestine 2	70.8	348.5
	ClnAC19	Colon 1	22.73	446.47
25	ClnAS12	Colon 2	116.97	493.18
	Kid106XD	Kidney 1	86.13	41.14
	Kid107XD	Kidney 2	0.26	35.14
	Lng47XQ	Lung 1	5.13	20.98
	Lng60XL	Lung 2	13.93	114.78
	Lng75XC	Lung 3	16.47	53.79
	Mam12X	Mammary Gland 1	6.25	10.75
	Mam162X	Mammary Gland 2	1.84	2.54
	Mam42DN	Mammary Gland 3	23.08	35.51

- 30 -

	Ovr10050	Ovary 1	0.9	
	Ovr1028	Ovary 2	261.4	
	Ovr103X	Ovary 3	7	0.1
	Ovr20GA	Ovary 4		0
5	Ovr25GA	Ovary 5		0

0 = Negative

Higher levels of expression were seen in prostate, showing a high degree of tissue specificity for prostate tissue. Of all the analyzed samples different from prostate, only two cancer samples (colon 2 with 116.97 and ovary 2 with 261.4 ), and 5 normal adjacent tissue samples (small intestine 2, colon 1, colon 2, kidney 1, and lung 2), showed an expression comparable to the mRNA expression in prostate. These results confirmed the tissue specificity results obtained with the panel of normal pooled samples (Table 7).

Furthermore, the levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 8 shows higher expression of Prol15 in 3 out of 4 matched prostate cancer tissues (prostate samples 1, 5 & 8).

Altogether, the high level of tissue specificity, plus the higher expression in 75% of the prostate matching samples tested, are indicative of Prol15 being a diagnostic marker for prostate cancer.

#### **Expression of Clone ID 3277219H1 (Prol10):**

For the CSG Prol10, real-time quantitative PCR was performed using the following primers:

Forward Primer

5' - CGGCAACCTGGTAGTGAGTG - 3' (SEQ ID NO:29)



- 31 -

## Reverse Primer

5'- CGCAGCTCCTTGTAAGTTCAG - 3' (SEQ ID NO:30)

The absolute numbers depicted in Table 9 are relative levels of expression of the CSG Prol10 in 12 normal different tissues. All the values are compared to normal small intestine (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

**Table 9: Relative Levels of CSG Prol10 Expression in Pooled Samples**

10

15

20

<b>Tissue</b>	<b>NORMAL</b>
Brain	6.61
Heart	0.7
Kidney	0.74
Liver	7.94
Lung	11.88
Mammary	22.78
Muscle	6.77
Prostate	3.01
Small Intestine	1
Testis	2.58
Thymus	13.74
Uterus	2.61

The relative levels of expression in Table 9 show that Prol10 mRNA expression is not as high in normal prostate (3.01) compared with all the other normal tissues analyzed.

The absolute numbers in Table 9 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 10.

The absolute numbers depicted in Table 10 are relative levels of expression of Prol10 in 33 pairs of matching samples. All the values are compared to normal small intestine (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from

- 32 -

the normal adjacent sample for that same tissue from the same individual.

**Table 10: Relative Levels of CSG Prol10 Expression in Individual Samples**

5	Sample ID	Tissue	Cancer	Matching Normal Adjacent
	Pro12B	Prostate 1	11.8	0.3
	Pro78XB	Prostate 2	14.3	6.3
	Pro101XB	Prostate 3	33.2	10.7
	Pro13XB	Prostate 4	0.3	0.4
10	Pro23XB	Prostate 5	25.5	14.4
	Pro20XB	Prostate 6	43.3	4
	Pro34XB	Prostate 7	31.8	18.7
	Pro65XB	Prostate 8	26.9	3.4
	Pro69XB	Prostate 9	12.5	7
15	Lng75XC	Lung 1	1.9	3
	Lng90X	Lung 2	5.5	0.5
	LngAC11	Lung 3	9.3	9.7
	LngAC32	Lung 4	11.2	2.2
	Lng47XQ	Lung 5	11.3	0.3
20	Lng60XL	Lung 6	29.1	6.8
	Mam12B	Mammary Gland 1	19.8	0
	Mam603X	Mammary Gland 2	13.7	0
	Mam82XI	Mammary Gland 3	73.5	0
	MamA04	Mammary Gland 4	0	24.6
25	MamB011X	Mammary Gland 5	17.4	2
	MamC012	Mammary Gland 6	0	12.8
	MamC034	Mammary Gland 7	0	61
	Mam12X	Mammary Gland 8	14	2.2
	Mam59X	Mammary Gland 9	33	2.2

- 33 -

	MamA06X	Mammary Gland 10	16.4	0.8
	Liv15XA	Liver 1	4.7	0.6
	Liv42X	Liver 2	7.5	2.6
	Liv94XA	Liver 3	0.4	1.4
5	ClnAS43	Colon 1	52.9	1.4
	ClnAS45	Colon 2	2.1	0.8
	ClnAS46	Colon 3	39.8	3.7
	SmI21X	Small Intestine 1	0.9	0.1
	SmIH89	Small Intestine 2	5.8	0.9

10 0 = Negative

The levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 10 shows overexpression of Prol10 in 8 of the 9 primary prostate cancer tissues compared with their respective normal adjacent (except prostate 4). Thus, there was overexpression in 88.88% of the cancer prostate tissue as compared to the prostate matching samples tested (total of 9 prostate matching samples).

Although not tissue specific, Prol10 mRNA expression is upregulated in prostate cancer tissues. The mRNA overexpression in 88.88% of the primary prostate matching cancer samples tested is indicative of Prol10 being a diagnostic marker for prostate cancer. Prol10 also showed overexpression in several other cancers tested including small intestine, colon, liver, mammary and lung (see Table 10). Accordingly Prol10 may be a diagnostic marker for other types of cancer as well.

- 34 -

**Expression of Clone ID 1857415; Gene ID 346880 (Prol13):**

For the CSG Prol13, real-time quantitative PCR was performed using the following primers:

Forward Primer

5' - CGGGAACCTACCAGCCTATG - 3' (SEQ ID NO:31)

Reverse Primer

5' - CAGGCAACAGGGAGTCATGT - 3' (SEQ ID NO:32)

The absolute numbers depicted in Table 11 are relative levels of expression of the CSG Prol13 in 12 normal different tissues. All the values are compared to normal thymus (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

**Table 11: Relative Levels of CSG Prol13 Expression in Pooled Samples**

<b>Tissue</b>	<b>NORMAL</b>
Brain	0.03
Heart	0
Kidney	0.01
Liver	0
Lung	0
Mammary Gland	0
Muscle	0.04
Prostate	489.44
Small Intestine	0.02
Testis	0.35
Thymus	1
Uterus	0.13

The relative levels of expression in Table 11 show that Prol13 mRNA expression is higher (489.44) in prostate compared with all the other normal tissues analyzed. Testis, with a relative expression level of 0.35, uterus (0.13), thymus (1.0), kidney (0.01) and brain (0.03) were among the other tissues expressing lower mRNA levels for Prol13. These results establish that Prol13 mRNA expression is highly specific for prostate.

- 35 -

The absolute numbers in Table 11 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 12.

The absolute numbers depicted in Table 12 are relative levels of expression of Prol13 in 78 pairs of matching and 25 unmatched tissue samples. All the values are compared to normal thymus (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. In cancers (for example, ovary) where it was not possible to obtain normal adjacent samples from the same individual, samples from a different normal individual were analyzed.

**Table 12: Relative Levels of CSG Prol13 Expression in Individual Samples**

Sample ID	Tissue	Cancer	Matched or Unmatched Normal Adjacent
Pro780B/781B	Prostate 1	375.58	446.29
Pro1291B/1292B	Prostate 2	1060	31
Pro139B96/140B96	Prostate 3	41	32
Pro209B96/210B96	Prostate 4	505	255
Pro1256B/1257B	Prostate 5	165.79	141.63
Pro1293B/1294B	Prostate 6	1613.7	874.61
Pro694B/695B	Prostate 7	458.6	142.21
Pro1012B/1013B	Prostate 8	1520	864
Pro1222B/1223B	Prostate 9	939	530
Pro845B/846B	Prostate 10	1552.4	374.6
Pro1094B/1095B	Prostate 11	278.37	135.89
Pro650B/651B	Prostate 12	532.81	640.85

- 36 -

	Pro902B/903B	Prostate 13	609.05	415.86
	Pro916B/917B	Prostate 14	699.42	401.24
	Pro9821110A/110B	Prostate 15	156	487.8
	ProS9821326A/26B	Prostate 16	744.4	472.8
5	Pro9407c215	Prostate 17	1389.2	
	Pro9407c234	Prostate 18	305.5	
	Pro9407c280A	Prostate 19	894.5	
	Pro9409C010R	Prostate 20 (prostatitis)	269.7	
	Pro9404C120R	Prostate 21 (prostatitis)	299.2	
10	Pro1000258	Prostate 22 (BPH)	149.6	
	Pro4001263C	Prostate 23 (BPH)	576	
	Pro4001267A	Prostate 24 (BPH)	132.1	
	Pro9411C032	Prostate 25 (BPH)	118.2	
	Pro4001460Z	Prostate 26 (BPH)	276.3	
15	Pro4001271A	Prostate 27 (BPH)	58.7	
	Kid1064D/65D	Kidney 1	0	0.1
	Kid1079D/1080D	Kidney 2	0.3	0.02
	Kid1097D/1098D	Kidney 3	35.14	0.32
	Kid1024D/1025D	Kidney 4	1.31	0
20	Kid1183D/1184D	Kidney 5	24.79	0
	Kid1242D/1243D	Kidney 6	0	0
	Bld469K	Bladder 1		2.88
	Bld467K/468K	Bladder 2	2.65	
	Bld327K/328K	Bladder 3	0	4.05
25	Bld470K	Bladder 4		1.64
	Bld665T/664T	Bladder 5	0.21	1.99

- 37 -

	Bld1496K/1497K	Bladder 6	13.55	1.14
	Bld1721K/1722K	Bladder 7	120.16	1.34
	Tst239X/240X	Testis 1	31.5	0.73
	TstS9820647A/47B	Testis 2	15.7	0
5	TstS9820663A/663B	Testis 3	72	1.4
	SknS9821248A/248B	Skin 1	1.8	0.5
	SknS99448A/448B	Skin 2	251.6	0
	Skn99816A/816B	Skin 3	33	0.7
	Sto4004864A4/B4	Stomach 1	14.12	0
10	Sto4004509A3/B1	Stomach 2	40.74	39
	SmI9807A212A/213A	Small Intestine 1	0.1	0
	SmI9802H008/H009	Small Intestine 2	5.8	0.1
	Cln9608B012/B011	Colon 1	4.5	0
	Cln9709c074ra/073ra	Colon 2	65.8	3.1
15	Cln4004709A1/709B1	Colon 3	1.1	0.9
	Cln9405C199/C200	Colon 4	34.76	0.73
	Cln9707c004gb/006ga	Colon 5	90.26	0.96
	Cln96-09-B004/B003	Colon 6	17.9	20.64
	Cln9612B006/B005	Colon 7	17.56	0.3
20	Cln9705F002D/F001C	Colon 8	21.39	0
	ClnCXGA	Colon 9	429.14	142.69
	Pan10343a	Pancreas 1	0	0
	Pan776P/777P	Pancreas 2	0	0.15
	Pan9210/9220	Pancreas 3	7.36	0
25	Pan714L/715L	Pancreas 4	13.57	0.11
	Pan824P/825P	Pancreas 5	0	0
	Lng476Q/477Q	Lung 1	0	0
	Lng605L/606L	Lung 2	0	0.1
	Lng11145B/11145C	Lung 3	85.9	0

- 38 -

	Lng0008632A/32B	Lung 4	23.85	0
	Lng750C/751C	Lung 5	0.32	0.25
	Lng8890A/8890B	Lung 6	10.63	0
	Lng8926A/8926B	Lung 7	15.37	0
5	Lng0010239A/39B	Lung 8	26.17	0
	Lng9502C109R/110R	Lung 9	0.68	0
	LngS9821944a/44b	Lung 10	0	0
	Mam00042D01/42N01	Mammary Gland 1	8.5	0
	Mam59XC	Mammary Gland 2	61.07	0
10	Mam9706A066G/67C	Mammary Gland 3	4.84	0
	Mam14153a1C	Mammary Gland 4	9.72	6.99
	Mam1620F/1621F	Mammary Gland 5	0.91	0
	Mam00014D05	Mammary Gland 6	2.45	0
	End10479B/D	Endometrium 1	133.43	1.12
15	End9705A125A/126A	Endometrium 2	0	0.39
	End9704C281A/282A	Endometrium 3	23.5	1.56
	End680o97/681o97	Endometrium 4	88.89	79.02
	Utr13590/13580	Uterus 1	0.2	0
	Utr850U/851U	Uterus 2	0	0
20	Utr14170/14180	Uterus 3	14	0.4
	Utr233U96/234U96	Uterus 4	8.65	4.64
	CvxVNM00052D01/52N01	Cervix 1	0.82	77.15
	CvxVNM00083D01/83N01	Cervix 2	0.78	221.48
	CvxND00023D01/23N01	Cervix 3	3.25	15.22
25	Ovr10370/10380	Ovary 1	0.1	0
	Ovr10050	Ovary 2	18.96	
	Ovr1028	Ovary 3	0	
	Ovr14638A1C	Ovary 4	3.2	
	Ovr14603A1D	Ovary 5	882.3	
30	Ovr7730	Ovary 6	0	



- 39 -

	Ovr9702C018GA	Ovary 7		0.15
	Ovr206I	Ovary 8		0
	Ovr9702C020GA	Ovary 9		0
	Ovr9702C025GA	Ovary 10		0
5	Ovr9701C035GA	Ovary 11		0.07
	Ovr9701C050GB	Ovary 12		0.58

0 = Negative

In the analysis of matching samples, the higher levels of expression were in prostate, showing a high degree of tissue specificity for prostate tissue. In addition to the higher expression levels in prostate cancer samples, Prol13 expression was found to be either induced (where not expressed in normal adjacent tissues) or somewhat upregulated in several other cancers. However, the relative expression and the fold increase in prostate cancer samples far exceeds that in other cancer tissues and is highly significant.

Furthermore, the levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 12 shows overexpression of Prol13 in 13 out of 16 primary prostate cancer tissues compared with their respective normal adjacent (prostate samples 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 16). Thus, there was overexpression in the cancer tissue for 81.25% of the prostate matching samples tested. The median for the level of expression in prostate cancer tissue samples is 609, whereas the median for all other cancers is only 7.93, with the exception of one colon sample, colon 9, whose expression was similar to that found in prostate cancer tissues.

Altogether, the high level of tissue specificity, plus the mRNA overexpression in 81.25% of the primary prostate matching samples tested are indicative of Prol13 being a

- 40 -

diagnostic marker for prostate cancer. Expression was also found to be higher in other cancer tissues compared with their respective normal adjacent tissues (kidney, bladder, testis, skin, stomach, small intestine, colon, pancreas, lung, mammary, endometrium, uterus, and ovary) thus indicating Prol13 to be a pan cancer marker.

**Expression of Clone ID 1810463H1 (Prol14):**

For the CSG Prol14, real-time quantitative PCR was performed using the following primers:

10 Forward Primer

5'- TGGGCATCTGGGTGTCAA - 3' (SEQ ID NO:33)

Reverse Primer

5'- CGGCTGCGATGAGGAAGTA - 3' (SEQ ID NO:34)

The absolute numbers depicted in Table 13 are relative levels of expression of the CSG Prol14 in 12 normal different tissues. All the values are compared to normal muscle (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

20 **Table 13: Relative Levels of CSG Prol14 Expression in Pooled Samples**

Tissue	NORMAL
Brain	9.7
Heart	0.7
25 Kidney	414.4
Liver	4
Lung	882.2
Mammary	44
Muscle	1
30 Prostate	1951
Small Intestine	22
Testis	367.1
Thymus	25.8
Uterus	139.6

35 The relative levels of expression in Table 13 show that Prol14 mRNA expression is higher (1951) in prostate compared with all the other normal tissues analyzed. Lung, with a relative

- 41 -

expression level of 882.2, kidney 414.4, testis 367.1 and uterus 139.6, are the other tissues expressing higher levels of mRNA for Prol14. These results establish Prol14 mRNA expression to be more specific for prostate than other tissues examined.

The high level of tissue specificity is indicative of Prol14 being a diagnostic marker for diseases of the prostate, especially cancer.

**Expression of Clone ID zr65g11 (Prol18):**

For the CSG Prol18, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- GCCCATCTCCTGCTTCTTTAGT - 3' (SEQ ID NO:35)

Reverse Primer

5'- CGTGGAGATGGCTCTGATGTA - 3' (SEQ ID NO:36)

The absolute numbers depicted in Table 14 are relative levels of expression of the CSG Prol18 in 12 normal different tissues. All the values are compared to normal kidney (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

**Table 14: Relative Levels of CSG Prol18 Expression in Pooled Samples**

<b>Tissue</b>	<b>NORMAL</b>
Colon	0.87
Endometrium	19282
Kidney	1
Liver	0
Ovary	86.22
Pancreas	0
Prostate	962.1
Small Intestine	0
Spleen	0.75
Stomach	0.54
Testis	343.7
Uterus	1064

- 42 -

The relative levels of expression in Table 14 show that Prol18 mRNA expression is the 3<sup>rd</sup> highest in prostate (962.1) next to endometrium (19282) and uterus (1064), which are female-specific tissues. Testis, with a relative expression level of 343.7 is the only other male tissue expressing moderate levels of mRNA for Prol18. These results establish Prol18 mRNA expression to be highly specific for reproductive tissues including the prostate.

The absolute numbers in Table 14 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 15.

The absolute numbers depicted in Table 15 are relative levels of expression of Prol18 in 59 pairs of matching and 21 unmatched samples. All the values are compared to normal kidney (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

**Table 15: Relative Levels of CSG Prol18 Expression in Individual Samples**

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Prol2B	Prostate 1	41700.7	22242.83
ProC234	Prostate 2	40087	
Pro78XB	Prostate 3	4075.6	7066.7
Pro109XB	Prostate 4	334.4	777.2
Pro84XB	Prostate 5	11684	58290
Pro101XB	Prostate 6	21474.13	100720.8
Pro91X	Prostate 7	14849	33717
Pro13XB	Prostate 8	202.57	146.91

- 43 -

	ProC215	Prostate 9	73243	
	Pro125XB	Prostate 10	629.6	521.4
	Pro23B	Prostate 11	157532.6	110654.4
	Pro90XB	Prostate 12	2317	64134
5	ProC280	Prostate 13	42020	
	Pro20XB	Prostate 14	2909.31	
	Pro34B	Prostate 15	29610	23264
	Pro110	Prostate 16	13354	30991
	Pro65XB	Prostate 17	10126	11270
10	Pro69XB	Prostate 18		2671.42
	Pro326	Prostate 19	9962.3	19231
	Pro10R	Prostate 20 (prostatitis)	27355	
	Pro20R	Prostate 21 (prostatitis)	21081	
	Pro258	Prostate 22 (BPH)	79916.32	
15	Pro263C	Prostate 23 (BPH)	108924.5	
	Pro267A	Prostate 24 (BPH)	92910.22	
	Pro271A	Prostate 25 (BPH)	57004.4	
	Pro460Z	Prostate 26 (BPH)	57449.23	
	ProC032	Prostate 27 (BPH)	45781.44	
20	Kid106XD	Kidney 1	3.08	217.36
	Kid107XD	Kidney 2	0	38.36
	Kid109XD	Kidney 3	0	123.5
	Kid10XD	Kidney 4	17.69	67.8
	Kid11XD	Kidney 5	16.74	360.8
25	Kid124D	Kidney 6	0	167.4
	Bld32XK	Bladder 1	0	0
	Bld47K	Bladder 2		36.38
	Bld66X	Bladder 3	0	4.52
	BldTR14	Bladder 4	0	12.17

- 44 -

	BldTR17	Bladder 5	0	0
	Bld46XK	Bladder 6	16.5	0
	Tst39X	Testis 1	116.6	24.35
	Tst647T	Testis 2	856.16	43.5
5	StoAC44	Stomach 1	0	0
	StoAC93	Stomach 2	0	0
	SmI21XA	Small Intestine 1	68.45	0
	SmIH89	Small Intestine 2	0	0
	ClnAC19	Colon 1	149	21.33
10	ClnAS12	Colon 2	0	0
	ClnB34	Colon 3	0	0
	ClnB56	Colon 4	13.04	5.22
	ClnAS43	Colon 5	0	0
	Lng47XQ	Lung 1	0	0
15	Lng60XL	Lung 2	0	0
	Lng75XC	Lung 3	0	3.38
	Lng90X	Lung 4	0	0
	LngBR26	Lung 5	0	26.82
	Pan10343	Pancreas 1	50.47	0
20	Pan77X	Pancreas 2	281.1	0
	Pan92X	Pancreas 3	18.41	0
	Pan71XL	Pancreas 4	0	0
	Pan82XP	Pancreas 5	0	0
	PanC044	Pancreas 6	0	0
25	Mam12X	Mammary Gland 1	0	0
	Mam162X	Mammary Gland 2	0	0
	Mam42DN	Mammary Gland 3	0	0
	MamS127	Mammary Gland 4	12.58	0
	Mam14DN	Mammary Gland 5	0	0
30	End28XA	Endometrium 1	331.9	1824

- 45 -

	End3AX	Endometrium 2	27825	65839
	End4XA	Endometrium 3	10.3	15935
	Utr141O	Uterus 1	18885	18116
	Utr23XU	Uterus 2	3358	7674
5	CvxKS52	Cervix 1	0	0
	CvxKS83	Cervix 2	0	0
	Ovr1005O	Ovary 1	72.86	
	Ovr1028	Ovary 2	0	
	Ovr638A	Ovary 3	0	
10	Ovr63A	Ovary 4	90.88	
	Ovr773O	Ovary 5	1.21	
	Ovr1040O	Ovary 6	5.08	
	Ovr105O	Ovary 7	0	
	Ovr1118	Ovary 8	7.41	
15	Ovr103X	Ovary 9		32.78
	Ovr20GA	Ovary 10		0
	Ovr25GA	Ovary 11		1173.83
	Ovr35GA	Ovary 12		313.4
	Ovr50GB	Ovary 13		823.1
20	Ovr18GA	Ovary 14		40.6
	Ovr206I	Ovary 15		1264
	Ovr230A	Ovary 16		1285

0 = Negative

In the analysis of matching samples, the higher levels of expression were in prostate, endometrium, testis, and ovary showing a high degree of tissue specificity for reproductive tissues. These results confirmed the tissue specificity results obtained with the panel of normal pooled samples (Table 14).

Furthermore, the levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an

- 46 -

indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 15 shows overexpression of Prol18 in 5 out of 14 primary prostate cancer tissues (prostate samples 1, 8, 5 10, 11, 15) compared with their respective normal adjacent. Thus, there was overexpression in the cancer tissue for 35.71% of the prostate matching samples tested (total of 14 prostate matching samples). Expression of Prol18 was similarly higher in 3 unmatched cancer tissues (prostate samples 9, 13, 14), 10 2 prostatitis (prostate samples 20, 21), and 6 benign hyperplasia tissues (prostate samples 22 through 27).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in 35.71% of the primary prostate matching samples tested are indicative of Prol18 being a 15 diagnostic marker for prostate cancer.



- 47 -

**What is claimed is:**

1. A method for diagnosing the presence of prostate cancer in a patient comprising:

(a) determining levels of CSG in cells, tissues or bodily fluids in a patient; and

(b) comparing the determined levels of CSG with levels of CSG in cells, tissues or bodily fluids from a normal human control, wherein a change in determined levels of CSG in said patient versus normal human control is associated with the presence of prostate cancer.

2. A method of diagnosing metastases of prostate cancer in a patient comprising:

(a) identifying a patient having prostate cancer that is not known to have metastasized;

(b) determining CSG levels in a sample of cells, tissues, or bodily fluid from said patient; and

(c) comparing the determined CSG levels with levels of CSG in cells, tissue, or bodily fluid of a normal human control, wherein an increase in determined CSG levels in the patient versus the normal human control is associated with a cancer which has metastasized.

3. A method of staging prostate cancer in a patient having prostate cancer comprising:

(a) identifying a patient having prostate cancer;

(b) determining CSG levels in a sample of cells, tissue, or bodily fluid from said patient; and

(c) comparing determined CSG levels with levels of CSG in cells, tissues, or bodily fluid of a normal human control, wherein an increase in determined CSG levels in said patient versus the normal human control is associated with a cancer which is progressing and a decrease in the determined CSG levels is associated with a cancer which is regressing or in remission.

- 48 -

4. A method of monitoring prostate cancer in a patient for the onset of metastasis comprising:

- (a) identifying a patient having prostate cancer that is not known to have metastasized;
- 5 (b) periodically determining levels of CSG in samples of cells, tissues, or bodily fluid from said patient; and
- (c) comparing the periodically determined CSG levels with levels of CSG in cells, tissues, or bodily fluid of a normal human control, wherein an increase in any one of the
- 10 periodically determined CSG levels in the patient versus the normal human control is associated with a cancer which has metastasized.

5. A method of monitoring a change in stage of prostate cancer in a patient comprising:

- 15 (a) identifying a patient having prostate cancer;
- (b) periodically determining levels of CSG in cells, tissues, or bodily fluid from said patient; and
- (c) comparing the periodically determined CSG levels with levels of CSG in cells, tissues, or bodily fluid of a normal
- 20 human control, wherein an increase in any one of the periodically determined CSG levels in the patient versus the normal human control is associated with a cancer which is progressing in stage and a decrease is associated with a cancer which is regressing in stage or in remission.

25 6. A method of identifying potential therapeutic agents for use in imaging and treating prostate cancer comprising screening molecules for an ability to bind to CSG wherein the ability of a molecule to bind to CSG is indicative of the molecule being useful in imaging and treating prostate cancer.

30 7. The method of claim 1, 2, 3, 4, 5 or 6 wherein the CSG comprises SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,

- 49 -

13, 14, 15, 16, 17, 18, 19 or 20 or a polypeptide encoded thereby.

8. An antibody which specifically binds CSG.

9. A method of imaging prostate cancer in a patient  
5 comprising administering to the patient an antibody of claim 8.

10. The method of claim 9 wherein said antibody is labeled with paramagnetic ions or a radioisotope.

11. A method of treating prostate cancer in a patient  
10 comprising administering to the patient an antibody of claim 7.

12. The method of claim 11 wherein the antibody is conjugated to a cytotoxic agent.

## SEQUENCE LISTING

<110> Salceda, Susana  
 Recipon, Herve  
 Cafferkey, Robert  
 diaDexus, LLC

<120> Method of Diagnosing, Monitoring, Staging, Imaging and  
 Treating Prostate Cancer

<130> DEX-0052

<140>

<141>

<150> 60/104,737

<151> 1998-10-19

<160> 36

<170> PatentIn Ver. 2.0

<210> 1

<211> 188

<212> DNA

<213> Homo sapiens

<400> 1

```

ggtaaacacc tgcttttatc atcagaacaa agaggctgtg tcccctgccc tatgagggtcc 60
atcttctgaga gttgtggcta atgggcaaga aggttggggc tttagagatt tgggataaag 120
atatcaaaca ccagaaaggt agaaagaagt gatcagatta ggggtactta ggtgatgata 180
tgaactct                                     188

```

<210> 2

<211> 9819

<212> DNA

<213> Homo sapiens

<400> 2

```

cagctggggt ctaccagggt ccatgtcttg gacatgttga gagtttttct ggaaggcagg 60
gatacagtgt ggtccaaaaa cacacaaatg cccctactgg ccagggggtt gtcacaatag 120
actggaaggg tgacacatcc caggcgcttg ccacccatca cacgcacctc ctaccactg 180
gcaccccttc accccaggca cacacaaagc ctcagtccag agatcaactc tggactcagc 240
tctgaatttg catatcctgt gtgtagattc attcttcata acctctgccc agcctagctt 300
gtgtatcatt tttttttctc tattagggga ggagcccgtc ctggcactcc cattggcctg 360
tagattcacc tcccctgggc agggccccag gaccaggat aatatctgtg cctcctgccc 420
agaaccttc aagcagacac aatggtaaga atggtgcctg tcctgctgtc tctgctgctg 480
cttctgggtc ctgctgtccc ccaggagaac caagatggtg agtggggaaa gcaagggatg 540

```

ggtgctggag aggactggaa ggaggtgagg aacaggacat gtggctggga gacaggctgg 600  
 atgcagctgg gataccctgg catacggcag gaatgggtgc ccaaggctgt caactccctc 660  
 agctcacaca cttccaggag cattcaggga gcctctgccc tggcccgaaa taagaccttc 720  
 aggaatctga atctaaaacc cctagtttac agtgaaaaca aagactccaa agaccaagcg 780  
 aectgcttgg ggtagacagt caggacggag taggaacctat atgcctggag ctgcttctgc 840  
 tctgttccct tccctccttc cgatggctgg gtacacctgc ctgacgctga ggaaaagaga 900  
 gagcagcccc aaggggaaag tgggaaggca ggttggctgg agggatgggt ctagaaggaa 960  
 acccgtgccc aaatcccaca ctcagacacc actgcagtgg gtctggaagg cgagtggctg 1020  
 gaagagaaga gagggggagc tccgggagat caagagtcac tcctaggata aggggaaggag 1080  
 gctgtttgtg gcatgagaat gtgcaggata aagacatgga agcgaatggc ttctcagttg 1140  
 tgtgagttta aaattcatga catttacaaa ttgtcagaaa aggtgttata tgtttgttat 1200  
 ataacaatca ctttggaaatg ttaattctgat tctgtgccaa aatctgaatt actcaggggt 1260  
 ctccagagaa acagaactaa taggtggtac acatatacat atatatgtac gtacacatac 1320  
 atacatacac tgtatacaca tggatacaca cacacatagg aagagattta catatatgta 1380  
 taaaaagag agagagagta gagatttatt ttaagaaatt gactcacact attgggagga 1440  
 gtaacaagtc ctaaattctc agagccggcc agcaggctgg agaccaggag aagagttgat 1500  
 gtcttagtct tgattccaag ggcagactgt aggcagaatt ctttcctctt taggggacat 1560  
 ctgaggcttt ttctcttaag gccttcaact gattggatga agcccaccac tatggagagt 1620  
 aatccacttt actcaaggtc tactgatttt tttgtaaatt aaaaaaaaaa ctgtgggtgc 1680  
 atagtatgtg tatatattta tggggtacat gagaggtttt gattcaggca tgcaatgtga 1740  
 aataatcaca tcatcaaaaa tgaggtatcc atccctcaa gcttttatcg tttgtgttac 1800  
 agacaatcca attatacttt tttggttatt ttagttttta aaagtatttg attatttatt 1860  
 tattttattt tttttgagac agagtctcac tctgtcacc aggcaggagt gcagtggcat 1920  
 gatctcggct cactgcaacc tccgcctccc aggttcaagc aattttcctg cctcagcttc 1980  
 ctgagtagct aggactacag gcacctgcca ccacacctgg ctaatttttt tgtattttta 2040  
 gtagagacgg tttcatcatg ttggccaggc tagtcttgat atcctgacct cgtgatctgc 2100  
 ccgccttggc ctcctcaagt gccgggatta cagggtgcag caactgcgcc tggcctctct 2160  
 tttggttatt taaaagtgtg caattaaatt atgattatta ttattatttt tgagatggat 2220  
 tcttgttctg tcaccaggc tggagtgcag tggcgtgatc ttggcttact gcaaacctcc 2280  
 gcctgttggg ttcaagcaat tatcttgctt cgggtgtaca ctgccacaca cggctaactt 2340  
 atgtattttt aatagagata ggggttcacc atgttggtta gactggtctt gacctcttga 2400  
 cctcaagtga tccactcact tcagcctccc agagtgcctg aattacaggc acgagccacc 2460  
 acacctggcc ccagttaaat tattattgac tatagtcacc ctgttgtgct atcaaatagt 2520  
 aggtcttatt cattcttctt tttttttttt tttttgtgac agagtggccc aggctggaat 2580  
 gcagtgggtc aatcttggct cactgcaacc tctgcctccc gggcttaagc gattctcctg 2640  
 cctcagcctt ctgagtcgct gggactacag gtgtgtgcca ccacgcccgg ctaatttatg 2700  
 tatttttagt agagatgggg tttcaccatg ttggccaggc tggtttcgaa ctctgacct 2760  
 caagtgacct acctgcctca gcttcccaa gtgttggaat tacaggcatg agccaccaca 2820  
 cctggcccca gttaaattat tattcactgg agtcactttg ttgtgctatc aaatagtttt 2880  
 ctaactattt tttttgtacc cattaaccac cctcccaatt tcccccaac cctgccacta 2940  
 ccttcccgag cctttggtta ccattcctct actctctatg tccatgaatt caattgtagg 3000  
 gtctactgat ttaaaggcta atcacattta gacactcagg agcaagaata atttttagtaa 3060  
 ttgaactagg attctgccat atgacctcca acatcattag cacctgtgta aattgtatca 3120  
 taaaataatt atggaactat tatggaaatg tccctctctc ccagatccca cttgtacca 3180  
 aaatgcaagg tacaaccccc ggaattctga gctccatcct agtcttacc tgtgctaatt 3240  
 cagtctgggt catttcttga attttctggt aaattctcct ttctaccctt tctaactata 3300  
 tgtatttctc aggttaagct agaagtgtta attttttttt tttttgagat ggagccttgc 3360  
 tttgtcacct aggtgaagt gcagtggcat gatctcagct cactgcaagc tccgcctccc 3420

ggggttcacgc cattctcctg cctcagcctc ctgagtagct gggactacag gcaccccgcca 3480  
 ccacgtcttg ctaatttttt gaattcttag tagagacggg gtttcacat gttagccagg 3540  
 atggtctcga tctcctgacc tcgtgatcca cccgcctcgg cccctctaaag tgctgggatt 3600  
 acaggcgtga gccactgagc ccggacgaaa tgttaatttg ttttttttga gacggagtct 3660  
 cactctgtca tccaagctgg agtgcagtgg catgatcttg gcttggtgca acctctgcct 3720  
 ctctggttca agtgattttc ctgcctcagc ctccagcatg actgggatta caggcccgca 3780  
 ccaccatgcc cagctaattt ttgtattttt taatagagat ggggtttcac catggttgcc 3840  
 aggtggtct tcaactcctg atctcaagta atctgcctgc cttggcctcc caaagtcctg 3900  
 ggattacagg catgagccac ggagcccagc ctagaaatgt taatttctaa cgcagtgcag 3960  
 attccatgca cactgggcaa ggttccattc ctccatgggg tgactcaggg atccaggcca 4020  
 attgcatatt gagactcttt catattatcc tgtggccttc aaagtcgtca cctctagga 4080  
 tgagaaacaa aagggaaagc cagctggtag ggtcttgac aagaagaaag acatcacttc 4140  
 tgctcacatt ctcttttgac aaaactcagt cacatggtcc caatatactc tcgaggtggc 4200  
 tgagtaatgt tatcttccta tgtgtcaagc agaggaaata atgtagtga gacacaggat 4260  
 ggtctctgaa atatcatctc aggcctgaaa gtagagcata ttcacttgag tgagcctcca 4320  
 gtggtgtgaa gttgatggca ggagaaagag ctggggaaga aaaggccagt ggcaggtctc 4380  
 cctcctagc cctatgcagc cccacagtgg gacccttgca tggacctcaa ccatcagaat 4440  
 cttttctttt gcaggtcgtt actctctgac ctatatctac actgggctgt ccaagcatgt 4500  
 tgaagacgtc cccgcgtttc aggccttggt ctcactcaat gacctccagt tctttagata 4560  
 caacagtaaa gacaggaagt ctcagcccat gggactcttg agacaggtgg aaggaatgga 4620  
 ggattggaag caggacagcc aacttcagaa ggccaggag gacatcttta tggagacct 4680  
 gaaagacatt gtggagtatt acaacgacag taacggtcag tgaataacag accacagggg 4740  
 tggaaggtct aaccaagag gcagccccc cagtgtgagt ggcaaggat cagcaggatg 4800  
 gaaatagtcc caatcccagg ggaagaacag gagacacagc agaaacacag acatgtccgc 4860  
 atcccccca cccacagca caggtgctcc ccgttcccc atcaattgcc ccatcctcat 4920  
 cccaggcctc aggtcacaca ggaagtgatg gcagagtcac ttcctatcca ggcacctatg 4980  
 acctctcacc tccacacccc acccatcgga ggtgatacc cccgtgagaa ggcacagac 5040  
 tcacccctgt ccaggagggt tgcttgaga gtgagccact ctcaaagtca ctcagacctg 5100  
 ggctcacctg gtggttctgc cagtcctagc tgttgacagt gaaacgttcc caaaatatct 5160  
 ggttgaaatc tgcaaacatt ggagcactga gacctacctc caaacaagtc tgtaatatct 5220  
 aactatgtct gttctatgaa ggatgtcaca gtctgtcctg atctcccttg cagctccatc 5280  
 acctagcaca gggtagagcc aatattggct caattgaaat ttgtggaatc cacagagaaa 5340  
 agcacccggc acacaccgta gcccatgctg ggggctcagg aagtgtgga ttcaaaactg 5400  
 tgggctgtta gagttccttg gagccctaaa gtctctcctt accatacgat gcagaccag 5460  
 gaagggccac ctgcgctatg gtcagaggag ctggtggcag agcccggtga gagatggtcc 5520  
 ctgtgcccc ggccagtgct tctttctcct aaaccacact gccagcccca aggcagccaa 5580  
 cctcaggtct ggtgaactgc tgggtgttaa ttatcataga gtgggtgtca aaagatgggc 5640  
 tactaagtac aaaaatgccc aaggtgtctac atgggatctg aagattttca aaaggaggca 5700  
 agaaagagat aggcagatgt ttcaaggatg tggggtgggg gaggtcttg taaggaaaat 5760  
 ggccagggct gtgtgtcagc aataggagag gagggggcac aggtgatcag aaaagacact 5820  
 gggggaagca ttgatggaca ggaatagaaa tggcaaagtg gataattaag aggaaggagg 5880  
 atgaggagat gaacacaggg tattagaaaa taatagaagg cagggttggt tggtcactc 5940  
 ttgtaatccc agcacttttg gaggtgagg caggcagatc acctaaagtc aggagttcga 6000  
 gaccagcccg gccacatgg tgaaacctg tcttactaa taatacaaaa atagcctggc 6060  
 atggtggcac acgtctgtgg tcccagctac tcaggaggct gaggcaggag aattgcttga 6120  
 acccaggagg cagaggttac agtgccaaa atcctaccat tgcactacag cctgggtgac 6180  
 aagagtga aa cgttgtctaa aaacaaaaa caaaaaacaa aaaaaggaaa taatagtagc 6240  
 tgacatttac tgagcactta cttgtgcca ggcccatcta tgagcatata taatgctcag 6300

aatagccccc taaaacagtg ctcttggcat tgccatttca gaggtgagga aatagaggca 6360  
 cagggagttg agtggctcca gttcaggcaa cacaccaggt gggggtgggg ggctggggag 6420  
 agacctggga cgtgagccca gacagcttga gagctttcag agtctatgcc aacagcacca 6480  
 accagtgctg ggtaaacacc tgctttttatc atcagaacaa agaggctgtg tccccgtccc 6540  
 tatgaggctc atttttgaga gttgtggcta atgggcaaga aggttggggc ttttagagatt 6600  
 tgggataaaag atatcaaaca ccagaaagggt agaaagaagt gatcagatta gggttactta 6660  
 ggtgatgata tgaactcttc ctagaactga gagaaaaaga gagccttcct ttactcatat 6720  
 gaaatcacaa ataatttcta tccaatttgg aagtacactt tgggtgtagtt gtgacagctt 6780  
 cctcaggact cagcataaat tcaaacaaat aattgtcctt agaagagatg ctatagaaga 6840  
 gatagaaata tattcatatt ctgtagcttt tttttttttg agatggagtt ttgctcttgt 6900  
 cacccaagct ggagtgcagt gatgcaatct cagctcactg caaactttgc ctcttgggtt 6960  
 caagggattc tcctgcctca gcctcccgat aactgggact acaggctaca ggcattgtgtc 7020  
 actactcctg gttaattttt tttttttttt ttttaagactg agtcttgctc tgtctttcag 7080  
 gctgatgtac aatggctcca tctcggtcca ctacaacttc tgtccccag gttcaagcga 7140  
 ttctcctgcc tcagcctcat gagtagctgg gattacaggc atgtgccagc acaccagca 7200  
 aatttttgta tttttagtag agatgaggtc ttaccatgtt ggccaggctg gtctcaaact 7260  
 cctgacctca ggtgatcctt tggcctcagc ctccctaact gctgggatta caggcatgag 7320  
 ccactgcgtc cagcctaatt ttatatTTTT ggtagagatg gggtttcacc atattggcca 7380  
 ggctgggtct gaactcatga cctaagggtga tccatcctcc tcagcctctc aaagtgtctg 7440  
 gattacaagt gtgagccact gggcctgggtg cttttttttt tttttttttt tttttttttt 7500  
 tgagataggg tctcactctg tcaccagggc tgaatgcag tagtgtgatt ttggctcatt 7560  
 gcagccttga cttccagggc tgaagtgatc ctcccacctc agcctcctga gtagctgggg 7620  
 ctacaggcat gcaccaccat gctgcgctaa ttttttatatt tttttagtg gtgggatttc 7680  
 gccatatcac cctggctgggt ctggaacccc tgggctcaag cgatccactc gcttcagctt 7740  
 ctcaaagtgc tgggattaca ggcattgagc acagcgccca ggctgtagct ctcttaagga 7800  
 ggaacatata tcatctgaga caaacctgaa atgccaaacc aaactgagtt agccctctc 7860  
 tgtctgttgt atatattgga gtaataacct atttgtcttg ataaagggat tgcattgttg 7920  
 aattgcaaaa acctttattt cttttgggtt gccaatgtg caagactaag agttattttg 7980  
 ataaatttct caccaggctg actgtctctc tgtggggctg ggggagtttt cagggtctca 8040  
 cgtattgcag ggaaggtttg gttgtgagat cgagaataac agaagcagcg gagcattctg 8100  
 gaaatattac tatgatggaa aggactacat tgaattcaac aaagaaatcc cagcctgggt 8160  
 ccccttcgac ccagcagccc agataaccaa gcagaagtgg gaggcagaac cagtctacgt 8220  
 gcagcggggc aaggcttacc tggaggagga gtgccctgcg actctgcgga aatacctgaa 8280  
 atacagcaaa aatatcctgg accggcaagg tactcactgc ttcctgctcc ccagtactga 8340  
 gccagaata aaagacgatc tcaggctagg agctcaggca acatcttagt ccggtctcat 8400  
 ctgttccttg atgtccctca gacccccagc tttcatcttt taggatttat tcttccctg 8460  
 ggataatata atttgtggtc caaaaagaac atcatcaaaa tttcaggcag aatgggccag 8520  
 gaaggccatt ctttcttgat gagtgtcccc aaatcatctc caattaacag acaaggagct 8580  
 tgaggttagg gaggtgaggg taacactgtc tgtaagaggc agagctggga ctcaaattcc 8640  
 agatttcaga ttccaaatcc catcggtttt tatctctaca atgatgcctc ccatctgggt 8700  
 ggtggagaga agggaggcgt gtaaaagtca gccccagaag gacaagagca agccagtgtg 8760  
 agcggaattg atggctgcaa gctgagactt ggattggaga cgtagtgaga ctcaggattg 8820  
 tgcagtgtg caggggaagt gttgtggat agaggcatgg gctgaaccaa gcagctggac 8880  
 tgagactggg ggacagaact ccaaagccca ctgagatgtg ggaaaacatg gagaagcaca 8940  
 cggagcattc acaacttatt gccgtcagag tcaatacatg ggtgaggtgg ggattgggca 9000  
 agagggaaag cgtcagcctt ccctgatatt ctggaaagtc tcccggggct gggggtgggc 9060  
 aggtacagag cttcagctc tgctgatcgc tgacatccag ggggtgggggt aggaagagac 9120  
 ctgggcccgg agaagtccac ctcaagcctg cagtgtcaca ctctatccct ccacagatcc 9180

```

tccctctgtg gtggtcacca gccaccaggc cccaggagaa aagaagaaac tgaagtgcct 9240
ggcctacgac ttctaccag ggaaaattga tgtgcactgg actcgggccg gcgaggtgca 9300
ggagcctgag ttacggggag atgttcttca caatggaaat ggcaattacc agtcctgggt 9360
ggtggtggca gtgccccgc agcacacagc cccctactcc tgccacgtgc agcacagcag 9420
cctggcccag cccctcgtgg tgcctggga ggccagctag gaagcaaggg ttggaggcaa 9480
tgtgggatct cagaccagc agctgccctt cctgcctgat gtgggagctg aaccacagaa 9540
atcacagtca atggatccac aaggcctgag gagcagtggt gggggacaga caggaggtgg 9600
atgtggagac cgaagactgg gatgcctgtc ttgagtagac ttggaccaa aaaatcatct 9660
caccttgagc ccacccccac ccattgtgt aatctgtaga agctaataaa taatcatccc 9720
tccttgccca gcataacaga gaatcctttt ttaacgggtg atgcgctgta gaaatgtgac 9780
tagattttct cattggttct gccctcaagc actgaattc 9819

```

&lt;210&gt; 3

&lt;211&gt; 250

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 3

```

cgccctgcg ccgccgagcc agctgccaga atgccgaact ggggaggagg caagaaatgt 60
ggggtgtgtc agaagacggg ttactttgcc gaagaggttc agtgcgaagg caacagcttc 120
cataaatcct gcttcctgtg catgggtctgc aagaagaatc tggacagtac cactgtggcc 180
gtgcatgggtg aggagattta ctgcaagtcc tgctacggca agaagtatgg gcccaaaggc 240
tatggctacg 250

```

&lt;210&gt; 4

&lt;211&gt; 1900

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (16)

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (18)

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (20)

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (1887)

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (1894)



&lt;400&gt; 4

```

acgccttccg cggagnanan caaaacggcg cgcaggccgg gcgcacccag ccgccacttc 60
cgagagcgcc tgccgcccct ggcgcccggc agccagctgc cagaatgccg aactggggag 120
gaggcaagaa atgtgggggtg tgtcaagaag acggtttact ttgccgaaga ggttcagtgc 180
gaaggcaaca gtttccataa atcctgcttc ctgtgcatgg tctgcaagaa gaatctggac 240
agtaccactg tgggcccgtg atggtgagga gatttactgg caagtccctg ctacggcaag 300
aagtatgggc ccaaaggcta tggctacggg ccaggggcga ggcaccctca gcaactgaca 360
gggggagtcg ctgggtatca agcacgagga agcccctggg ccacaggccc accaccaacc 420
ccaatggcat ccaaatttgc ccagaagatt ggtggctccg agcgtgccc ccgatgcagc 480
caggcagtc atgctgcgga gaagggtgatt ggtgctggga agtccctggc taaggcctgc 540
tttcgatgtg ccaagtgtgg caaaggcctt gagtcaacca ccctgggcag acaaggatgg 600
cgagatttac tgcaaaggat gttatgctaa aaacttcggg cccaagggtt ttggttttgg 660
gcaaggagct ggggccttgg tccactctga gtgaggccac catcaccac cacaccctgc 720
ccactcctgc gcttttcatc gccattccat tcccagcagc tttggagacc tccaggatta 780
tttctctgtc agccctgcca catatcacta atgacttgaa cttgggcac tggctccctt 840
tgggttgggg gtctgcctga ggtcccaccc cactaaaggg ctccccaggc ctgggatctg 900
acaccatcac cagtaggaga cctcagtgtt ttgggtctag gtgagagcag gccctctcc 960
ccacacctcg cccacagag ctctgttctt agcctcctgt gctgctgtc catcatcagc 1020
tgaccaagac acctgaggac acatcttggc acccagagga gcagcagcaa caggctggag 1080
ggagagggaa gcaagacca gatgaggagg ggggaaggct gggttttttg gatctcagag 1140
attctcctct gtgggaaaga ggttgagctt cctggtgtcc ctcagagtaa gcctgaggag 1200
tcccagctta gggagtccac tattggaggc agagaggcat gcaggcaggg tcctaggagc 1260
ccctgcttct ccaggcctct tgcctttgag tctttgtgga atggatagcc tcccactagg 1320
actgggagga gaataaccca ggtcttaagg accccaaagt caggatgttg tttgatcttc 1380
tcaaacatct agttccctgc ttgatgggag gatcctaag aaatacctga aacatatatt 1440
ggcatttate aatggctcaa atcttcattt atctctggcc ttaaccctgg ctccctgaggc 1500
tgcggccagc agagcccagg ccagggtctt gttcttgcca cacctgcttg atcctcagat 1560
gtggagggag gtaggcactg cctcagtctt catccaaaca cctttccctt tgccctgaga 1620
cctcagaatc ttccctttaa cccaagacct tgccctcttc actccaccct tctccaggga 1680
cccttagatc acatcactcc acccctgcca gggcccagg taggaatagt ggtgggagga 1740
aggggaaagg gctgggcctc accgctccca gcaactgaaa ggacaacact atctggagcc 1800
accactgaa agggctgcag gcatgggctg tacccaagct gattttctcat ctggtcaata 1860
aagctgttta gaccagaaaa aaaaaanaaa aaanaaaagg 1900

```

&lt;210&gt; 5

&lt;211&gt; 273

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 5

```

gatgcatcaa aagagctgca agttctccac attgacttct tgaatcagga caacgccgtt 60
tctcaccaca catgggagtt ccaaacgagc agtccctgtg tccggcgagg acagggtgtt 120
cacctgcggc tgggtgctga ccagccccta caatcctacc accaactgaa actggaattc 180
agcacagggc cgaatcctag catcgccaaa cacaccctgg tgggtgctga cccgaggacg 240
ccctcagacc actacaactg gcaggcaacc ctt 273

```

&lt;210&gt; 6

&lt;211&gt; 3021

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 6

tgtggaagca ccaggcatca gagatagagt cttccctggc attgcaggag agaactctgaa 60  
gggatgatgg atgcatcaaa agagctgcaa gttctccaca ttgacttctt gaatcaggac 120  
aacgccgttt ctcaccacac atgggagttc caaacgagca gtcctgtgtt ccggcgagga 180  
caggtgtttc acctgcggct ggtgctgaac cagcccctac aatcctacca ccaactgaaa 240  
ctggaattca gcacagggcc gaatcctagc atcgccaaac acaccctggg ggtgctcgac 300  
ccgaggacgc cctcagacca ctacaactgg caggcaaccc ttcaaaatga gtctggcaaa 360  
gaggtcacag tggctgtcac cagttcccc aatgccatcc tgggcaagta ccaactaaac 420  
gtgaaaactg gaaaccacat ccttaagtct gaagaaaaca tcctatacct tctcttcaac 480  
ccatggtgta aagaggacat ggttttcatg cctgatgagg acgagcgcaa agagtacatc 540  
ctcaatgaca cgggctgcca ttacgtgggg gctgccagaa gtatcaaatg caaaccttg 600  
aactttggtc agtttgagaa aaatgtcctg gactgctgca tttccctgct gactgagagc 660  
tcctcaagc ccacagatag gagggacccc gtgctggtgt gcagggccat gtgtgctatg 720  
atgagctttg agaaaggcca gggcgtgctc attgggaatt ggactgggga ctatgaagg 780  
ggcacagccc catacaagtg gacaggcagt gcccgatcc tgcagcagta ctacaacacg 840  
aagcaggctg tgtgttttgg ccagtgtgtg gtgtttgtgt ggatcctgac tacagtgtgt 900  
agagcgttgg gcatcccagc acgcagtgtg acaggcttcg attcagctca cgacacagaa 960  
aggaacctca cgggtggacac ctatgtgaat gagaatggca agaaaatcac cagtatgacc 1020  
cacgactctg tctggaattt ccatgtgtgt acggatgcct ggatgaagcg accggatctg 1080  
cccaagggtc acgacggctg gcaggtgtg gacgcaacgc cgcaggagcg aagccagggt 1140  
gtcttctgct gtgggccatc accactgacc gccatccgca aagggtgacat ctttattgtc 1200  
tatgacacca gattcgtctt ctcagaagtg aatgggtgaca ggctcatctg gttgggtgaag 1260  
atggtgaatg ggcaggagga gttacacgta atttcaatgg agaccacaag catcgggaaa 1320  
aacatcagca ccaaggcagt gggccaagac aggcggagag atatcaccta tgagtacaag 1380  
tatccagaag gtcctcttga ggagaggcag gttcatggat catgccttcc tccttctcag 1440  
ttctgagagg gagcacagac gacctgtaaa agagaacttt cttcacatgt cgggtacaatc 1500  
agatgatgtg ctgctgggaa actctgttaa tttcaccgtg attcttaaaa ggaagaccgc 1560  
tgccctacag aatgtcaaca tcttgggctc ctttgaacta cagttgtaca ctggcaagaa 1620  
gatggcaaaa ctgtgtgacc tcaataagac ctgcgagatc caaggtcaag tatcagaagt 1680  
gactctgacc ttggactcca agacctacat caacagcctg gctatattag atgatgagcc 1740  
agttatcaga ggtttcatca ttgcggaat tgtggagtct aaggaaatca tggcctctga 1800  
agtattcacg tctttccagt accctgagtt ctctatagag ttgcctaaca caggcagaat 1860  
tggccagcta cttgtctgca attgtatctt caagaatacc ctggccatcc ccttgactga 1920  
cgtcaagtct tctttggaaa gcctgggcat ctcctcacta cagacctctg accatgggtg 1980  
agtctgcctg aggacggtgc agcctggtga gaccatccaa tcccaaataa aatgcacccc 2040  
aataaaaatg gacccaagaa atttatcgtc aagttaaagt ccaaacaagt gaaagagatt 2100  
aatgctcaga agattgttct catcaccaag tagccttgtc tgatgctgtg gagccttagt 2160  
tgagatttca gcatttccta ccttgtggct tagctttcag attatggatg attaaatttg 2220  
atgacttata tgagggcaga ttcaagagcc agcaggtcaa aaaggccaac acaaccataa 2280  
gcagccagac ccacaaggcc aggtcctgtg ctatcacagg gtcaccttct ttacagtta 2340  
gaaacaccag ccgagggcac agaatcccat ccctttcctg agtcatggcc tcaaaaatca 2400  
gggccaccat tgtctcaatt caaatccata gatttcgaag ccacagattc tctccctgga 2460  
gcaagcatga ctatgggcag ccagtgctg ccacctgctg acgacccttg agaagctgcc 2520  
atatcttcag gccatgggtt caccagccct gaaggcacct gtcaactgga gtgctctctc 2580

```

agcactggga tgggcctgat agaagtgcac tctcctccta ttgcctccat tctcctctct 2640
ctatccctga aatccaggaa gtccctctcc tgggtctcca agcagtttga agcccaatct 2700
gcaaggacat ttctcaaggg ccatgtgggt ttgcagacaa ccctgtccctc aggcctgaac 2760
tcaccataga gaccatgtc agcaaacggg gaccagcaaa tctcctctccc ttattctaaa 2820
gctgccctt gggagactcc agggagaagg cattgtctcc tccctgggtgt gaactctttc 2880
tttggtatcc catccactat cctggcaact caaggctgct tctgttaact gaagcctgct 2940
ccttcttggt ctgccctcca gagatttgct caaatgatca ataagcttta aattaaaactc 3000
tacttcaaga aaaaaaaccc g
3021

```

&lt;210&gt; 7

&lt;211&gt; 267

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 7

```

gaacattcca gatacctatc attactcgat gctgttgata acagcaagat ggctttgaac 60
tcagggtcac caccagctat tggaccttac tatgaaaacc atggatacca accggaaaac 120
ccctatcccg cacagcccac tgtgggtcccc actgtctacg aggtgcatcc ggctcagtac 180
taccggtccc ccgtgccccg gtacgccccg agggtcctga cgcaggcttc caaccccgtc 240
gtctgcacgc agcccaaata cccatcc
267

```

&lt;210&gt; 8

&lt;211&gt; 3443

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 8

```

gggcgggccg ggccgagtag gcgcgagcta agcaggaggc ggaggcggag gcgaggggcg 60
agggcggggg agcgccgcct ggagcgcggc aggtcatatt gaacattcca gatacctatc 120
attactcgat gctgttgata acagcaagat ggctttgaac tcagggtcac caccagctat 180
tggaccttac tatgaaaacc atggatacca accggaaaac ccctatcccg cacagcccac 240
tgtgggtcccc actgtctacg aggtgcatcc ggctcagtac taccggtccc ccgtgccccg 300
gtacgccccg agggtcctga cgcaggcttc caaccccgtc gtctgcacgc agcccaaata 360
cccatccggg acagtgtgca cctcaaagac taagaaagca ctgtgcatca ccttgacct 420
ggggaccttc ctctgtgggag ctgcgctggc cgctggccta ctctggaagt tcatgggcag 480
caagtgtctc aactctggga tagagtgcga ctctcagggt acctgcatca accctctaa 540
ctgggtgtgat ggcgtgtcac actgccccg cggggaggac gagaatcggg gtgttcgct 600
ctacggacca aacttcatcc ttcagggtgta ctcatctcag aggaagtctt ggcacctgt 660
gtgccaagac gactggaacg agaactacgg gcgggcggcc tgcagggaca tgggtataa 720
gaataatatt tactctagcc aaggaatagt ggatgacagc ggatccacca gctttatgaa 780
actgaacaca agtgccggca atgtcgatat ctataaaaaa ctgtaccaca gtgatgcctg 840
ttcttcaaaa gcagtgggtt ctttacgctg tatagcctgc ggggtcaact tgaactcaag 900
ccgccagagc aggatcgtgg gcggcgagag cgcgctcccc ggggcctggc cctgggcagg 960
tcagcctgca cgtccagaac gtccacgtgt gcggaggctc catcatcacc ccgagtgga 1020
tcgtgacagc cgtccactgc gtggaaaaac ctcttaacaa tccatggcat tggacggcat 1080
ttgcggggat tttagacaa tctttcatgt tctatggagc cggataccaa gtagaaaaag 1140
tgatttctca tccaaattat gactccaaga ccaagaacaa tgacattgct ctgatgaagc 1200
tgcagaagcc tctgactttc aacgacctag tgaaccaggt gtgtctgccc aaccaggga 1260

```

```

tgatgctgca gccagaacag ctctgctgga tttccgggtg gggggccacc gaggagaaag 1320
ggaagacctc agaagtgtg aacgctgcca aggtgttct cattgagaca cagagatgca 1380
acagcagata tgtctatgac aacctgatca caccagccat gatctgtgcc ggcttcctgc 1440
aggggaacgt cgattcttgc cagggtgaca gtggagggcc tctggtcact tcgaagaaca 1500
atatctggtg gctgatagg gatacaagct ggggttctgg ctgtgccaaa gcttacagac 1560
caggagtgtg cgggaatgtg atgggtattca cggactggat ttatcgacaa atgagggcag 1620
acggctaata cacatgggtc tcgtccctga cgtcgtttta caagaaaaca atggggctgg 1680
ttttgcttcc ccgtgcatga tttactctta gagatgattc agaggctact tcatttttat 1740
taaacagtga acttgtctgg ctttggcact ctctgccatt ctgtgcaggc tgcagtggct 1800
ccctgccca gcctgtctc cctaaccctc tgtccgcaag ggggtgatggc cggctgggtg 1860
tgggcaactg cggtaagtgt tggaggagag ggggtggaggc tgccccattg agatcttcct 1920
gctgagtcct ttccaggggc caattttgga tgagcatgga gctgtcacct ctcagctgct 1980
ggatgacttg agatgaaaaa ggagagacat ggaaagggag acagccaggc ggcacctgca 2040
gcggctgcct ctggggccac ttggtagtgt cccagccta cctctccaca aggggatttt 2100
gctgatgggt tcttagagcc ttagcagccc tggatgggtg ccagaaataa agggaccagc 2160
ccttcagggg tggtagctgt gtagtcacct tgtaagggga acagaaacat tttgttctt 2220
atggggtgag aatatagaca gtgcccttgg gtgcgaggga agcaattgaa aaggaaactg 2280
ccctgagcac tcctgggtgca ggtctccacc tgcacattgg gtggggctcc tgggaggag 2340
actcagcctt cctcctcatc ctccctgacc ctgctcctag caccctggag agtgcacatg 2400
cccttggtc ctgggcaggg gcgccaagtc tggcaccatg ttggcctctt caggcctgct 2460
agtcactgga aattgaggtc catgggggaa atcaaggatg ctcagttaa ggtacactgt 2520
ttccatgtta tgtttctaca cattgctacc tcagtgtcc tggaaactta gcttttgatg 2580
tctccaagta gtccacctc atttaactct ttgaaactgt atcatctttg ccaagtaaga 2640
gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa cgttctataa 2700
atgaatgtgc tgaagcaaag tgcccatggt ggcgcgaaag aagagaaaga tgtgttttgt 2760
tttgactct ctgtgttccc ttccaatgct gtgggtttcc aaccagggga agggctccct 2820
ttgcattgcc aagtgccata accatgagca ctactctacc atggttctgc ctccctggca 2880
agcaggtggt tttgcaagaa tgaatgaat gattctacag ctaggactta accttgaaat 2940
ggaaagtctt gcaatcccat ttgcaggatc cgtctgtgca catgcctctg tagagagcag 3000
cattcccagg gaccttgga acagttggca ctgtaagggt cttgctcccc aagacacatc 3060
ctaaaagggt ttgtaatggt gaaaacgtct tccttcttta ttgccccctt ttatttatgt 3120
gaacaactgt ttgtcttttt ttgtatcttt tttaaactgt aaagttcaat tgtgaaaatg 3180
aatatcatgc aaataaatta tgcgattttt ttttcaaagt aacctgca tctttgaagt 3240
tctgcctggt gagtaggacc agcctccatt tccttataag ggggtgatgt tgaggctgct 3300
ggtcagagga ccaaagggtg ggcaaggcca gacttggtgc tcctgtggtt ggtgcctca 3360
gttcctgcag cctgtcctgt tggagaggtc cctcaaatga ctcttctta ttattctatt 3420
agtctgttcc catgggcgtg ata 3443

```

&lt;210&gt; 9

&lt;211&gt; 254

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 9

```

gtgctgcacc aggccaccat cctgccaag actgggacag tgtccctgga ggtacggctc 60
ctggaggcct cccgtgcctt cgagggtgtc gagaacggca acctggtagt gagtgggaag 120
gtgtaccagt gggatgacct tgacccagg ctcttcgacc acccgaaaag cccaccccc 180
aaccacacgg agccccctt cctggcccag gctgaagttt acaaggagct gcgtctgcgt 240

```

ggctacgact acgg

254

&lt;210&gt; 10

&lt;211&gt; 8470

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (4131)

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (5117)

&lt;220&gt;

&lt;221&gt; unsure

&lt;222&gt; (5552)

&lt;400&gt; 10

cggccgctcga cacggcagcg gccccggcct ccctctccgc cgcgcttcag cctcccgctc 60  
cgccgcgctc cagcctcgct ctccgccgce cgcaccgceg cccgcgccct caccagagca 120  
gccatggagg aggtggtgat tgccggcatg tccgggaagc tgccagagtc ggagaacttg 180  
caggagtctt gggacaacct catcggcggt gtggacatgg tcacggacga tgaccgtcgc 240  
tggaaggcgg ggctctacgg cctgccccgg cggctccggca agctgaagga cctgtctagg 300  
tttgatgcct ccttcttcgg agtccacccc aagcaggcac acacgatgga cctcagctg 360  
cggctgctgc tggaagtac ctatgaagcc atcgtggacg gaggcataca cccagattca 420  
ctccgaggaa cacacactgg cgtctgggtg ggcgtgagcg gctctgagac ctccgaggcc 480  
ctgagccgag accccgagac actcgtgggc tacagcatgg tgggctgcca gcgagcgatg 540  
atggccaacc ggctctcctt cttcttcgac ttcagagggc ccagcatcgc actggacaca 600  
gcctgctcct ccagcctgat ggccctgcag aacgcctacc aggccatcca cagcgggcag 660  
tgccctgccg ccacgtggg gggcatcaat gtcctgctga agcccaacac ctccgtgcag 720  
ttcttgaggc tggggatgct cagccccgag ggcacctgca aggccttcga cacagcgggg 780  
aatgggtact gccgctcgga ggggtgtggtg gccgtcctgc tgaccaagaa gtccctggcc 840  
cggcgggtgt acgccaccat cctgaacgcc ggcaccaata cagatggctt caaggagcaa 900  
ggcgtgacct tccccacagg ggatatccag gagcagctca tccgctcgtt gtaccagtcg 960  
gccggagtgg cccctgagtc atttgaatac atcgaagccc acggcacagg caccaagggtg 1020  
ggcgaccccc aggagctgaa tggcatcacc cgagccctgt gcgccacccg ccaggagccg 1080  
ctgctcatcg gctccaccaa gtccaacatg gggcacccgg agccagcctc ggggctggca 1140  
gccttgccca aggtgctgct gtccctggag cacgggctct gggcccccaa cctgcacttc 1200  
catagcccca accctgagat cccagcgtg ttggatgggc ggctgcaggt ggtggaccag 1260  
cccctgcccg tccgtggcgg caacgtgggc atcaactcct ttggcttcgg gggctccaaa 1320  
cgtgcacatc atcctgaggc ccaacacgca gccgcccccc gcacccggcc cacatgccac 1380  
cctgccccgt ctgctgcggg ccagcggacg cacccttgag gccgtgcaga agctgctgga 1440  
gcagggcctc cggcacagcc agggcctggc tttcctgagc atgtgaacga catcgcggtc 1500  
gtccccgacc accgccatgc ccttccgtgg ctacgctgtg ctgggtggtg agacgcgggtg 1560  
gccagagggt gcagcagggt cccgctggcg agcgcgccgt ctggttcacg tgctctggga 1620  
tgggcacaca gtggcgcggg atggggctga gcctcatgcg cctggaccgc ttccgagatt 1680

ccatcctacg ctccgatgag gctgtgaacc gattcggcct gaagggtgtca cagctgctgc 1740  
 tgagcacaga cgagagcacc tttgatgaca tcgtccattc gtttgtgagc ctgactgcca 1800  
 tccagatagg cctcatagac ctgctgagct gcatggggct gaggccagat ggcacgtcg 1860  
 gccactcctt gggggagggtg gcctgtggct acgccgacgg ctgcctgtcc caggaggagg 1920  
 ccgtcctcgc tgcctactgg aggggacagt gcatcaaaga agcccatctc ccg<sup>\*</sup>ccgggcg 1980  
 ccatggcagc cgtgggcttg tcctgggagg agtgtaaaca gcgctgcccc ccggcggtgg 2040  
 tgcccggcgc cacaactcca aggacacagt caccatctcg ggacctcagg ccccggtgtt 2100  
 tgagttcgtg gagcagctga ggaaggaggg tgtgtttgcc aaggagggtg ggaccggcg 2160  
 tatggccttc cactcctact tcatggaggc catcgcaccc ccactgtgc aggagctcaa 2220  
 gaagggtgac cgggagccga agccacgttc agcccgctgg ctgagcacct ctatccccga 2280  
 ggcccagtggt cacagcagcc tggcacgcac gtcctccgcc gagtacaatg tcaacaacct 2340  
 ggtgagccct gtgctgttcc aggaggccct gtggcacgtg cctgagcacg cgggtgtgtc 2400  
 ggagatcgcg cccacgccc tgcctgagc tgcctgaag cgtggcctga agccgagctg 2460  
 caccatcatc cccctgatga agaaggatca cagggacaac ctggagtctt tcctggccgg 2520  
 catcggcagg ctgcacctct caggcatcga cgccaacccc aatgccttgt tcccacctgt 2580  
 ggagtcccca gctccccgag gaactccctt catctcccca ctcatcaagt gggaccacag 2640  
 cctggcctgg gacgcgccgg ccgccgagga cttccccaac gggtcaggtt cccctcagc 2700  
 caccatctac acatgcacac caagctccga gtctcctgac cgctacctgg tggaccacac 2760  
 catcgacggg cgcgtcctct tccccgccac tggctacctg agcatagtgt ggaagacgct 2820  
 ggcccgaccc ctgggcctgg gcgtcgagca gctgcctgtg gtgtttgagg atgtggtgct 2880  
 gcaccaggcc accatcctgc ccaagactgg gacagtgtcc ctggaggtag ggctcctgga 2940  
 ggcctccgtt gccttcgagg tgtcagagaa cggcaacctg gtagtgagtg ggaagggtgt 3000  
 ccagtgggat gacctgacc ccaggctctt cgaccacccg gaaagcccca ccccaaccc 3060  
 cacggagccc ctctcctcgg ccaggctga agtttacaag gagctgcgtc tgcgtggcta 3120  
 cgactacggc cctcatcttc agggcatcct ggaggccagc ctggaagggt actcggggag 3180  
 gctgctgtgg aaggataatg ggtgagttca tggacacat gctgcagatg tccatcctgg 3240  
 gtcggccaag cacggcctgt acctgcccac ccgtgtcacc gccatccaca tcgacctgc 3300  
 caccacagc cagaagctgt acacactgca ggacaaggcc caagtggctg acgtgggtgt 3360  
 gagcaggtgg ctgagggtca cagtggccgg aggcgtccac atctccgggc tccacactga 3420  
 gtcggccccc cgccggcagc agggagcagc ggtgcccac ctggagaagt tttgcttcac 3480  
 tccccacacg gaggaggggt gcctgtctga gcacgtgcc ctcgaggagg agctgcaact 3540  
 gtgcaagggg ctggtcgagg cactcgagac caaggtgacc cagcaggggc tgaagatggt 3600  
 ggtgcccgga ctggatgggg cccagatccc cccgggaccc ctcacagcag gaactgcccc 3660  
 ggctgttgtc ggctgcctgc aggttccagc tcaacgggaa cctgcagctg gagctggcgc 3720  
 aggtgctggc ccaggagagg cccaagctgc cagaggaccc tctgctcagc ggctcctgg 3780  
 actccccggc actcaaggcc tgcttgagca ctgctgtgga gaacatgccc agcctgaaga 3840  
 tgaagggtgt ggagggtgtg gccggccacg gtcacctgta tccccgcatc ccaggcctgc 3900  
 tcagccccc tccccgtctg cagctgagct acacggccac cgaccgccac cccaggccc 3960  
 tggaggctgc ccaggccgag ctgcagcagc acgacgttgc ccaggggccag tgggatcccc 4020  
 cagacctgc cccagcgcc ctgggcagcg cggacctcct ggtgtgcaac tgtgctgtgg 4080  
 ctgccctcgg ggaccgcct cagctctcag caacatggtg gctgccctga nagaaggggg 4140  
 ctttctgctc ctgcacacac tgcctcgggg gcaccccctc ggggacatcg tggccttctc 4200  
 cacctccact gagccgcagt atggccaggg catcctgagc caggacgcgt gggagagcct 4260  
 cttctccagg gtgtcgctgc gcctgggtgg cctgaagaag tcttctacg gctccacgt 4320  
 cttcctgtgc cgccggccca ccccgagga cagcccatc ttctgcccgg tggacgatac 4380  
 cagcttccgc tgggtggagt ctctgaaggg catcctggct gacgaagact ctttccggc 4440  
 ctgtgtggct gaaggccatc aactgttcca cctcgggcgt ggtgggcttg gtgaactgtc 4500  
 tccgcccaga gcccgcgga acgctccggt gtgtgctgct ctccaacctc agcagcacct 4560

cccacgtccc ggaggtggac ccgggctccg cagaactgca gaaggtgttg cagggagacc 4620  
 tggatgatgaa cgtctaccgc gacggggcct ggggggcttt ccgccacttc ctgctggagg 4680  
 aggacaagcc tgaggagccg acggcacatg cctttgtgag caccctcacc cggggggacc 4740  
 tgccctcca tccgctgggt ctgctcctcg ctgcccctg cccagcccac ctgcccctggc 4800  
 gcccagctct gcacggtcta ctacgcctcc ctcaacttcc gcgacatcat gctggccact 4860  
 ggcaagctgt cccctgatgc catcccaggg aagtggacct cccaggacag cctgctaggt 4920  
 atggagttct cgggcccaga cggcagcggc aagcgtgtga tgggactggg gcctgccaaag 4980  
 ggctggcca cctctgtcct gctgtcaccg gacttcctct gggatgtgcc ttccaactgg 5040  
 acgctggagg agggggcctc ggtgcctgtc gtctacagca cggcctacta cgcgctggtg 5100  
 gtgctggggc ggggtgcncct cggggagacg ctgctcatcc actcgggctc gggcggcgtg 5160  
 ggccaggccg ccatcgccat cggcctcagt ctgggctgcc gcgtcttcac caccgtgggg 5220  
 tcggctgaga agcgggctga cctccaggcc aggttcccc agctcgacag caccagcttc 5280  
 gccaactccc gggacacatc cttcgagcag catgtgctgt ggcacacggg cgggaagggc 5340  
 gttgacctgg tcttgaactc cttggcggaa gagaagctgc agggcagcgt gaggtgcttg 5400  
 gctacgcacg gtcgcttctt ggaaattggc aaattcgacc tttctcagaa ccaccgctc 5460  
 ggcattggcta tcttcttgaa gaacgtgaca ttccacgggg tctactgga tgcgttcttc 5520  
 aacgagagca gtgctgactg gcgggaggtg tnggcgcttg tgcaggccgg catccgggat 5580  
 ggggtggtac ggccctcaa gtgcacggtg ttccatgggg cccagggtgga ggacgccttc 5640  
 cgctacatgg cccaagggaa gcacattggc aaagtcgtcg tgcagggtgct tgcggaggag 5700  
 ccggaggcag tggctgaagg gggccaaacc caagctgatg tcggccatct ccaagacctt 5760  
 ctgcccggcc cacaagagct acatcatcgc tgggtgtctg ggtggcttcg gcctggagtt 5820  
 ggcgcagtgg ctgatacagc gtgggggtga gaagctcgtg ttgacttctc gctccgggat 5880  
 ccggacaggc taccaggcca agcaggtccg ccggtggagg cggcaggcg tacagggtga 5940  
 ggtgtccacc agcaacatca gctcactgga gggggcccgg ggcctcattg ccgaggcgcc 6000  
 gcagcttgag gcccggtggc ggcgtcttca acctggccgt ggtcttgaga gatggcttgc 6060  
 tggagaacca gacccagag ttcttccagg acgtctgcaa gcccaggtac agcggcacc 6120  
 tgaacctgga cagggtgacc cgaggcggtg cctgagctg gactactttg tggcttcttc 6180  
 ctctgtgagc tgcggcggtg gcaatgcggg acagagcaac tacggctttg ccaatttccg 6240  
 ccatggagcg tatctgtgag aaacgccggc acgaaggcct cccaggcctg gccgtgcagt 6300  
 ggggcgccat cggcgacgtg ggcatttttg tggagacgat gagcaccaac gacacgatcg 6360  
 tcagtggcac gctgccccag cgcattggct cctgcctgga ggtgctggac ctcttctga 6420  
 accagcccca catggtcctg agcagctttg tgctggctga gaaggctgcg gcctataggg 6480  
 acagggacag ccagcgggac ctggtggagg ccgtggcaca catcctgggc atccgcgact 6540  
 tggctgctgt caacctggac agctcactgg cggacctggg cctggactcg ctcatgagcg 6600  
 tggagggtgc ccagacgctg gagcgtgagc tcaacctggt gctgtccgtg cgcgagggtg 6660  
 ggcaactcac gctccgaaa ctgcaggagc tgctctcaa ggcggatgag gccagcgagc 6720  
 tgggcatgcc ccacgcccga ggaggatggt ctggcccagc agcagactca gctgaacctg 6780  
 cgctccctgc tgggtgaacct ggaggggccc acctgatgc ggctcaactg ccgtgcagag 6840  
 ctcgagcgcg cccctgttcc tgggtgacct aattcgagg ctccaccacc gtgttccaca 6900  
 gcctggcctc ccggctcagc atccccacct atggcctgca gtgcacccga gctgcgcccc 6960  
 ttgacagcat ccacagcctg gctgcctact acatcgactg catcaggcag gtgcagcccc 7020  
 agggccctca ccgctggcc ggctactcct acggggcctg cgtggccttt gaaatgtgct 7080  
 cccagctgca ggcccagcag agcccagccc ccaccacaa cagcctcttc ctgttcgacg 7140  
 gctcggccac ctacgtactg gcctacacct agagctaccg ggcaaagctg accccaggct 7200  
 gtgaggctga ggctgagacg gaggccatat gcttcttctg gcagcagttc acggacatgg 7260  
 agcacaacag ggtgctggag gcgctgctgc cgctgaaggg cctagaggag cgtgtggcag 7320  
 ccgctgtgga cctgatcatc aagagccacc agggcctgga ccgccaggag ctgagctttg 7380  
 cggcccggtc cttctactac aagctgcgtg ccgctgagca gtacacaccc aaggccaagt 7440

```

accatggcaa cgtgatgcta ctgctgcca agacgggtgg cgcctacggc gaggacctgg 7500
gcgcggacta caacctctcc caggtagcg acgggaaagt atccgtccac gtcacgagg 7560
gtgaccaccg cacgctgctg gagggcagcg gcctggagtc catcatcagc atcatccaca 7620
gtcccttggc tgagccacgc gtgagcgtgc gggagggcta ggcccgtgcc cccgcctgcc 7680
accggaggtc actccaccat cccacccca tccacccca ccccgccat gcaacgggat 7740
tgaagggtcc tgccgggtgg accctgtccg gccagtgcc actgcccccc gaggctagct 7800
agacgtaggt gttaggcatg tccacccac ccgcgcctc ccacggcacc tcggggacac 7860
cagagctgcc gacttggaga ctcttgtct gtgaagagcc ggtggtgccc gtgcccgcag 7920
gaactggggc tgggcctcgt gcgcccgagg ggtctgcgct tggctcttct gtgcttgat 7980
ttgcatattt attgcattgc tggtagagac cccaggcct gtccaccctg ccaagactcc 8040
tcaggcagcg tgtgggtccc gcactctgcc cccatttccc cgatgtcccc tgcgggcgcg 8100
ggcagccacc caagcctgct ggctgcggcc cctctcggc caggcattgg ctccagccgc 8160
tgagtggggg gtcgtggggc agtccccgag gactggggcc ctgcacaggc acacagggcc 8220
cgccacacc cagggccccc ccgcacagcc acccggtggg tgctgccctt atgccggcg 8280
ccgggcacca actccatgtt tgggtgttct ctgtgttct ttttcaagaa atgattcaaa 8340
ttgtgcttg gattttgaaa tttactgtaa ctgtcagtg acacgtctgg acccggttcc 8400
atctttacac caatttggtt aaaatgctgc tctcagcctc ccacaattaa accgcatgtg 8460
atctccaaaa                                     8470

```

&lt;210&gt; 11

&lt;211&gt; 812

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 11

```

gccgcagcca atcagcgcgc gtgcccgggc ccctgcgtct cttgcgtcaa gacggccgtg 60
ctgagcgaat gcaggcgact tgcgagctgg gagcgattta aaacgctttg gattcccccg 120
gcctgggtgg ggagagcgag ctgggtgccc cctagattcc ccgccccgc acctcatgag 180
ccgacctctg gctccatgga gcccggcaat tatgccacct tggatggagc caaggatatc 240
gaaggcttgc tgggagcggg agggggcgcg aatctggtcg cccactcccc tctgaccagc 300
caccagcgg cgcctacgct gatgcctgct gtcaactatg ccccttgga tctgccaggc 360
tcggcgagc gccaaagcaa tgccaccat gccctgggtg gcccagggg acgtccccag 420
ctcccgtgcc ttatggttac tttggaggcg ggtactactc ctgccgagtg tcccggagct 480
cgctgaaacc ctgtgcccag gcagccacc tggccgcgta ccccgcgag actccacgg 540
ccggggaaga gtacccagc cggccactg agtttgctt ctatccggga tatccgggaa 600
cctaccagcc tatggccagt tacctggacg tgtctgtggt gcagactctg ggtgctcctg 660
gagaaccgag acatgactcc ctgttgctg tggacagtta ccagtcttgg gctctcgctg 720
gtggctggaa cagccagatg tgttgccagg gagaacagaa cccaccaggc ccttttggaa 780
aggcagcatt tgcagactcc agcgggcagc ac                                     812

```

&lt;210&gt; 12

&lt;211&gt; 2385

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 12

```

ataagctggg gtaaagtatt ttcgcagttt ctgcctttag gattttatta gcttctctcc 60
cccaggccgc agccaatcag cgcgcgtgcc cgggcccctg cgtctcttgc gtcaagacgg 120

```



```

ccgtgctgag cgaatgcagg cgacttgcca gctgggagcg atttaaaacg ctttggattc 180
ccccggcctg ggtggggaga gcgagctggg tgccccctag attccccgcc cccgcacctc 240
atgagccgac cctcggctcc atggagcccc gcaattatgc caccttggat ggagccaagg 300
atatcgaagg cttgctggga gcgggagggg ggcggaatct ggtcgccac tccccctctga 360
ccagccaccc agcggcgccct acgctgatgc ctgctgtcaa ctatgcccc ttggatctgc 420
caggctcggc ggagccgcca aagcaatgcc acccatgccc tggggtgccc caggggacgt 480
ccccagctcc cgtgccttat ggttactttg gaggcgggta ctactcctgc cgagtgtccc 540
ggagctcgct gaaaccctgt gcccaggcag ccaccctggc cgcgtacccc gcggagactc 600
ccacggcccg ggaagagtac ccagccgcc cactgagtt tgccctctat ccgggatata 660
cgggaacctt ccagcctatg gccagttacc tggacgtgtc tgtggtgcag actctgggtg 720
ctctggaga accgcgacat gactccctgt tgctgtgga cagttaccag tcttgggctc 780
tcgtggtggt ctggaacagc cagatgtgtt gccagggaga acagaacca ccaggtccct 840
tttgaaggc agcatttgca gactccagcg ggcagcacc tctgacgcc tgcgcctttc 900
gtcgcggccg caagaaacgc attccgtaca gcaaggggca gttgcgggag ctggagcggg 960
agtatgcggc taacaagttc atcaccaagg acaagaggcg caagatctcg gcagccacca 1020
gcctctcgga gcgccagatt accatctggt ttcagaaccg ccgggtcaaa gagaagaagg 1080
ttctcgccaa ggtgaagaac agcgctaccc cttaagagat ctcttgccct ggggtggagg 1140
agcgaagtgt ggggtgtcct ggggagacca ggaacctgcc aagcccaggc tggggccaag 1200
gactctgctg agaggcccct agagacaaca cccttcccag gccactggct gctggactgt 1260
tcctcaggag cggcctgggt acccagtatg tgcagggaga cggaaaccca tgtgacagcc 1320
cactccacca gggttcccaa agaacctggc ccagtcataa tcattcatcc tgacagtggc 1380
aataatcacg ataaccagta ctagctgcca tgatcgtag cctcataatt tctatctaga 1440
gctctgtaga gcactttaga aaccgctttc atgaattgag ctaattatga ataaatttgg 1500
aaggcgatcc ctttgcaggg aagctttctc tcagaccccc tccattaca cctctcacc 1560
tggtaacagc aggaagactg aggagagggg aacgggcaga ttcgttgtgt ggctgtgatg 1620
tcctgttagc atttttctca gctgacagct gggtaggttg acaattgtag aggctgtctc 1680
ttctccctc cttgtccacc ccatagggtg taccactgg tcttgaagc accatccct 1740
aatacgatga tttttctgtc gtgtgaaaat gaagccagca ggctgcccct agtcagtcct 1800
tccttccaga gaaaaagaga tttgagaaag tgcctgggta attcaccatt aatttcctcc 1860
cccaaactct ctgagtcttc ccttaatat tctggtggtt ctgaccaaag caggtcatgg 1920
tttgttgagc atttgggac ccagtgagt agatgtttgt agccttgcat acttagccct 1980
tcccaggcac aaacggagtg gcagagtgtt gccaacctg ttttcccagt ccacgtagac 2040
agattcacgt gcggaattct ggaagctgga gacagacggg ctctttgcag agccgggact 2100
ctgagagggg catgagggcc tctgcctctg tgttcattct ctgatgtcct gtacctgggc 2160
tcagtggccg gtgggactca tctcctggcc gcgcagcaa gccagcgggt tcgtgctggt 2220
ccttctgca ccttaggctg ggggtggggg gcctgccggc gcattctcca cgattgagcg 2280
cacaggcctg aagtctggac aaccgcaga accgaagctc cgagcagcg gtcggtggcg 2340
agtagtgggg tcggtggcga gcagtgggtg gtgggccgcg gccgc 2385

```

&lt;210&gt; 13

&lt;211&gt; 221

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

```

dsdnrstatc tttctgtgtg gtgcagccct gttggcagt ggcactctgg tgtcaatcga 60
tggggcatcc tttctgaaga tcttcgggcc actgtctgcc agtgccatgc agtttgtcaa 120
cgtgggctac ttctcatcg cagccggcgt tgtggtcttt gctcttggtt tctgggctg 180

```

ctatggtgct aagactgaga gcaagtgtgc cctcgtgacg t

221

&lt;210&gt; 14

&lt;211&gt; 1533

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

```

gggcacgcag acattctggg aagccacttg cccacccctt gggctgcttc ttcttgagat 60
caggaggggc gttgcccagg gctgggtgtg ccagggtggag gctgctgag gcagtgggtg 120
tggggatcgg tctccaggca gcagggggca gcagggtcaa ggagaggcta actggccacg 180
gggtggggcca gcaggcgggc agaaggaggc tttaaagcgc ctaccctgcc tgcagggtgag 240
cagtgggtgtg tgagagccag gccgtccctc tgcctgccc ctcagtggca acaccggga 300
gctgttttgt cctttgtgga gcctcagcag ttccctgctt tcagaactca ctgccaaagag 360
ccctgaacag gagccaccat ggcagtgtct cagcttcatt aagaccatga tgatcctctt 420
caatttgctc atctttctgt gtggtgcagc cctgttggca gtgggcatct ggggtgtcaat 480
cgatggggca tcctttctga agatcttcgg gccactgtcg tccagtggca tgcagtttgt 540
caacgtgggc tacttctca tcgcagccgg cgttgtggtc tttgctcttg gtttcctggg 600
ctgctatggt gctaagactg agagcaagtg tgcctcgtg acgttcttct tcatcctcct 660
cctcatcttc attgctgagg ttgcagctgc tgtggtcgcc ttggtgtaca ccacaatggc 720
tgagcacttc ctgacgttgc tggtagtgcc tgccatcaag aaagattatg gttcccagga 780
agacttcact caagtgtgga acaccaccat gaaagggctc aagtgtgtg gcttcaccaa 840
ctatacggat tttgaggact caccctactt caaagagaac agtgccttct cccattctg 900
ttgcaatgac aacgtcacca acacagccaa tgaacctgc accaagcaaa aggtcacga 960
ccaaaaagta gaggttgct tcaatcagct tttgtatgac atccgaacta atgcagtcac 1020
cgtgggtggt gtggcagctg gaattggggg cctcgagctg gctgccatga ttgtgtccat 1080
gtatctgtac tgcaatctac aataagtcca cttctgcctc tgccactact gctgccacat 1140
gggaactgtg aagaggcacc ctggcaagca gcagtgattg ggggagggga caggatctaa 1200
caatgtcact tgggccagaa tggacctgcc cttctgtctc cagacttggg gctagatagg 1260
gaccactcct ttaggcgat gcctgacttt ccttccattg gtgggtggat ggggtggggg 1320
cattccagag cctctaaggt agccagttct gttgccatt cccccagtct attaaacct 1380
tgatatgccc ctaggccta gtggtgatcc cagtgtctca ctgggggatg agagaaaggc 1440
attttatagc ctgggcataa gtgaaatcag cagagcctct ggggtggatgt gtagaaggca 1500
cttcaaatg cataaacctg ttacaatgtt gcc 1533

```

&lt;210&gt; 15

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 15

```

tcagagaaaa ctcaaacttt attgagagaa ttttcaaatt ttcagtcaca ttttcaatgt 60
gacatcagcc atgtgtgtag cttcagcttg tcttcttttt aacttatggc tgcccactct 120
ctgcttcttt agtcttagca tgcttaggat taggtggagt cttctctttt acatcagagc 180
catctccacg ctactccga gtcttttcca gatccatttc ctggcaatca cttctactt 240
tacgttcttc gatcggaggt gttccttctc tctcttgtcc aggttcaata tctgattgt 300
cagttgggtg ttctcttgc tgagattcac cgggagccac gaatgcaacc acatcgggag 360
cctcctgacc atctctctt cctctggatc ttgatctcac tcgtgcactc atcgtgcaa 420

```

ctagaagatc gtgaactgaa gaacttgagt cagcagagag cctggcgaag aa 472

<210> 16

<211> 478

<212> DNA

<213> Homo sapiens

<400> 16

cttcattctt cgccaggctc tctgctgact caagttcttc agttcacgat cttctagttg 60  
cagcgatgag tgcacgagtg agatcaagat ccagaggaag aggagatggg caggaggctc 120  
ccgatgtggg tgcattcgtg gctcccgggtg aatctcagca agaggaacca ccaactgaca 180  
atcaggatat tgaacctgga caagagagag aaggaacacc tccgatcgaa gaacgtaaag 240  
tagaagggtga ttgccaggaa atggatctgg aaaagactcg gagtgagcgt ggagatgggt 300  
ctgatgtaaa agagaagact ccacctaata ctaagcatgc taagactaaa gaagcaggag 360  
atgggcagcc ataagttaaa aagaagacaa gctgaagcta cacacatggc tgatgtcaca 420  
ttgaaaatgt gactgaaaat ttgaaaatc tctcaataaa gtttgagttt tctctgaa 478

<210> 17

<211> 198

<212> DNA

<213> Homo sapiens

<220>

<221> unsure

<222> (191)

<400> 17

cccgtgtac cccccagca tgttctgctc cggcggaggg caagaccaga aggactcctg 60  
caacgggtgac tctggggggc cctgatctg caacgggtac ttgcagggcc ttgtgtcttt 120  
cggaaaagcc ccgtgtggcc aagttggcgt gccagggtgc tacaccaacc tctgcaaatt 180  
cactgagtggt nattaagg 198

<210> 18

<211> 465

<212> DNA

<213> Homo sapiens

<400> 18

tggagatgga gtatgtatctt attttacaaa aataaatcac catcttcgga ccattttag 60  
actggaacat ttcgagcaat gagtgcgcca cacggacgag tgccctggtg actccctgat 120  
gttcgctca cccccaggc cacttggcg ccgcatgag cctcgcttcc cactcccggc 180  
ctccaactcc ctccctcgc agccgccatt cacttctgc tgtttatctg tctgcagagc 240  
gcctggacac cggaaaaggc gattccctga gcgcctggag ttggagacaa ttcttggttc 300  
agaatttaaa catctttcta aggtaagcgc tgctccaaa ctcttcgccg cgtggggact 360  
ttgcaccagg ggcggttggg aaggaaagtg gccctccacg ggctcctggg caaccgcggc 420  
ctgttgaaaa aaggttcttg gtcaaataat ttaacttcgg aggag 465

<210> 19

<211> 204  
 <212> DNA  
 <213> Homo sapiens

<400> 19  
 ggcggaaca ggcgcgctg gacctgtacc cctacgacgc cgggacggac agcggcttca 60  
 ccttctctc cccaacttc gccaccatcc cgcaggacac ggtgaccgag ataacgtcct 120  
 cctctcccag ccaccggcc aactccttct actaccgcg gctgaaggcc ctgcctccca 180  
 tcgccagggt gacactggtg cggc 204

<210> 20  
 <211> 294  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> unsure  
 <222> (287)

<400> 20  
 gagatttctc ttcaatggct tcctgtgagc tagagtttga aaatatctta aaatcttgag 60  
 ctagagatgg aagtagcttg gacgatttct attatcatgt aaatcgggtc actcaagggg 120  
 ccaaccacag ctgggagcca ctgctcaggg gaaggttcat atgggacttt ctactgcccc 180  
 aggttctata caggatataa aggtgcctca cagtatagat ctggtagcaa agtaagaaga 240  
 aacaaacact gatctcttct tgccaccctc ctgacccttt ggaactnctc tgac 294

<210> 21  
 <211> 22  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:Synthetic

<400> 21  
 atcagaacaa agaggctgtg tc 22

<210> 22  
 <211> 21  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:Synthetic

<400> 22  
 atctctaaag cccaacctt c 21

<210> 23  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 23  
tgccgaagag gttcagtgc 19

<210> 24  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 24  
gccacagtgg tactgtccag at 22

<210> 25  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 25  
gctgcaagtt ctccacattg a 21

<210> 26  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 26  
cagccgcagg tgaaacac 18

<210> 27  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Synthetic

<400> 27

tggctttgaa ctcagggta

20

<210> 28

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Synthetic

<400> 28

cggatgcacc tcgtagacag

20

<210> 29

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Synthetic

<400> 29

cggcaacctg gtagtgagtg

20

<210> 30

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Synthetic

<400> 30

cgcagctcct tgtaaacctc ag

22

<210> 31

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Synthetic

<400> 31  
cgggaaccta ccagcctatg 20

<210> 32  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 32  
caggcaacag ggagtcattgt 20

<210> 33  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 33  
tgggcatctg ggtgtcaa 18

<210> 34  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 34  
cggctgcgat gaggaagta 19

<210> 35  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:Synthetic

<400> 35  
gcccatctcc tgcttcttta gt 22

<210> 36

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

<400> 36

cgtggagatg gctctgatgt a

21



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/24331

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 141.1, 155.1, 183.1; 435/6, 7.1, 7.23, 7.9, 91.2; 436/501, 504, 505, 547; 514/44; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Medline, Biosis, Embase, Cancerlit, Scisearch, WPIDS, USPATFULL  
search terms: CSG, cancer specific gene, cancer, diagnosis**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SCISEARCH, Accession Number 307617, OLSSON et al. Reverse transcriptase-polymerase chain reaction assays for prostate cancer. Urologic Clinics of North America. May 1997, Vol. 24 No. 2, pages 367-&.	1-6
Y	CHO-CHUNG et al. Antisense Oligonucleotides for the treatment of cancer. Current Opinion in Therapeutic Patents. 1993, Vol. 3, No. 12, pages 1737-1750, see entire document.	1-6
A,E	BUSSEMAKERS et al. DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Research. 01 December 1999, Vol. 59, No. 23, pages 5975-5979.	1-7

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 FEBRUARY 2000

Date of mailing of the international search report

07 MAR 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Authorized officer

GEETHA P. BANSAL

Facsimile No. (703) 305-3230

Telephone No. (703) 308-0196

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US99/24331

**A. CLASSIFICATION OF SUBJECT MATTER:**

IPC (7):

A61K 39/395, 48/00; C12P 19/34; C12Q 1/68; G01N 33/53, 33/574, 33/546, 33/567

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL :

424/130.1, 141.1, 155.1, 183.1; 435/6, 7.1, 7.23, 7.9, 91.2; 436/501, 504, 505, 547; 514/44; 536/23.5